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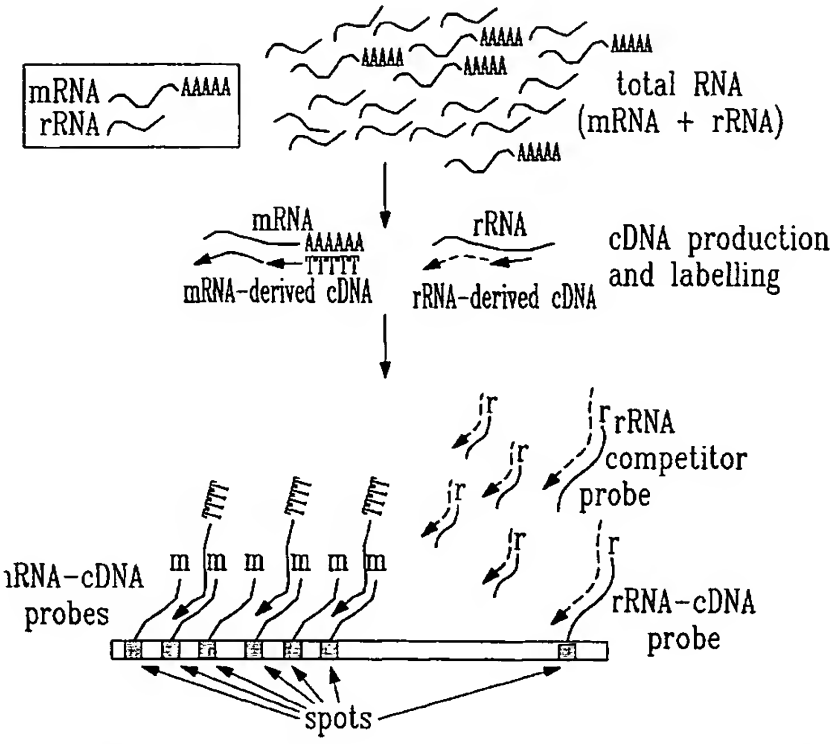
(54) Title: METHOD FOR NORMALIZING THE RELATIVE INTENSITIES OF DETECTION SIGNALS IN HYBRIDIZATION ARRAYS



(57) Abstract: The present invention relates to rRNA-derived cDNA used as an internal standard or control to achieve normalization of hybridization signal detection in microarray biochip technology. Analysis of data obtained from a laser scanner during DNA microarray experiments first requires image processing. However, the data generated for the arrayed genes must be normalized before differentially expressed genes can be identified. Normalization is necessary to compensate for differences in labelling and detection efficiencies for the labels and for differences in the quantity of starting RNA from the samples examined in the assay. Because of its relatively invariant expression across tissues and treatments, 18S and 28S ribosomal RNAs are ideal internal controls for quantitative RNA analysis. A way to circumvent the technical difficulties of using ribosomal RNA as a ...rol, because of its overabundance relative to that of other RNAs, is described and claimed in the present application. Impr... methods, arrays and kits comprising arrays and free unlabelled ribosomal probes, are objects of this invention. The unlab... ribosomal probes are used to compete out the excess or ribosomal nucleics present in a sample wherein all cDNA species of the ...ple are labelled before being placed in contact with the arrays.

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TITLE OF THE INVENTION

Method for Normalizing the Relative Intensities of Detection Signals in Hybridization Arrays

FIELD OF THE INVENTION

The present invention relates to the field of hybridization arrays. More specifically, the present invention concerns a method for normalizing signals to be compared in hybridization arrays. This novel method relies on the use of ribosomal RNA (rRNA) as an internal standard and allows approximation of the relative abundance of multiple mRNAs as well as direct comparisons between any two specific RNA samples.

BACKGROUND OF THE INVENTION

In DNA microarray experiments, one of the more popular ways to control for spotted DNA quantity and surface chemistry anomalies involves the use of two-color fluorescence (see refs. 4, 5). For example, a Cy3 (green)-labelled probe prepared from healthy tissue could be used as a control to examine expression profiles of a Cy5 (red)-labelled probe prepared from a tumor tissue. The normalized expression values for every gene would then be calculated as the ratio of experimental expression to control expression. This method can obviously eliminate much (but not all) experimental variation by allowing two samples to be compared on the same chip because there is enough DNA on each spot that both test and reference cDNAs can hybridize to it at once without interference. More sophisticated three-color experiments are also possible in which one channel serves as a control for the amount of spotted DNA, and channels two and three allow two samples to be compared to this control and to each other (see ref. 5).

In addition to the local normalization method described above, more general methods are also available in the form of control spots on the slide. With a set of control spots, it is possible to control variations in overall slide quality or scanning differences.

Applicable normalization strategies are based on some underlying assumptions regarding the data and the strategies used for each experiment. These strategies must therefore be adjusted to reflect both the system under study and the experimental design. A primary assumption is that for either an entire collection of arrayed genes or some subset of the genes (such as housekeeping genes), or for some added set of controls, the ratio of measured expression averaged over the set should be close to unity.

The need for good methods of normalisation for microarray data can not be overstated (see refs. 6, 7). Depending on the experimental design, there are three useful approaches for calculating normalization factors. The first simply relies on the total fluorescent intensity measured. The assumption underlying this approach is that the total mass of RNA labelled with either Cy3 or Cy5 is equal. While the intensity for any one spot may be higher in one channel than the other, when averaged over thousands of spots in a given array, these fluctuations average out. Consequently, the total integrated intensity across all the spots in the array should be equal for both channels. Alternatively, one could add a number of controls in increasing but equimolar concentrations to both labeling reactions, and the sum of the intensities for these spots should be equal.

A second approach uses linear regression analysis. For closely related samples, one would expect many of the genes to be expressed at nearly constant levels. Consequently, a scatter plot of the measured Cy5 versus Cy3 intensities should have a slope of one. Measured intensities for added equimolar controls should behave similarly. Under this assumption, one can use regression analysis techniques to calculate the slope which is used to rescale the data and adjust the slope to one.

A third approach has been described by Chen et al (1997) (ref. 1). In it, it is assumed that a subset of housekeeping genes exists and that for these genes the distribution of transcription levels should have some mean value and standard deviation that are independent of any particular sample. In this case, the ratio of measured Cy5 to Cy3 ratios for these genes can be modeled and the mean of the ratio adjusted to 1. Chen and his collaborators describe an iterative procedure to achieve this normalization. Quackenbush and collaborators (ref. 2) have implemented their own algorithm and a variation

thereof that uses the entire data set in a data visualization and analysis tool called TIGR ArrayViewer. Other statistical methods of determining data accuracy have been described (ref. 3, 11).

The above procedures describe array-based measures that can be used to normalize data. However, even with multiple colour fluorescence and control spots, undesired experimental variation can contaminate expression data. It is also possible that some or all of the physical normalization techniques are missing from the experiment, in which case it is even more important to find additional means of normalization.

The use of internal standards overcomes these problems. Using an exogenously added standard has the advantage of giving the user absolute control over the amount of template added, with no variation between samples. Using an exogenous standard does not, however, control differences in the quality of the starting RNA in a reverse transcription reaction. If there are differences in the levels of integrity of the RNA between otherwise identical samples, the yield of specific reverse transcriptase products will reflect this variation, although the external standards will still appear identical. For this reason, as well as for simplicity and reproducibility, an endogenous RNA standard should be favoured in microarray experiments.

Theoretically, an ideal endogenous standard for a DNA microarray would be a transcript whose expression does not vary during the cell cycle, between cell types, or in response to the experimental treatments that one wishes to examine. Additionally, for an endogenous standard to be valid in a microarray it is crucial that it be of a similar relative abundance as the test and reference (or target) transcripts in the microarray. Unfortunately, such a molecule does not exist and there are serious limitations to the standards currently in use. For example, although beta-actin is a frequently used standard (refs 9, 10), its level of expression varies significantly from tissue to tissue.

For DNA microarray experiments, mRNA is copied into cDNA with the use of reverse transcriptase so that the relative abundance of individual mRNAs is reflected in the cDNA product. Input RNA in reverse transcription reactions is usually quantified by spectrophotometry. The RNA that is used in a typical pre-reverse transcription reaction is total RNA, 80% of which is ribosomal RNA. The mRNA component of total cellular RNA can vary from 2% to 5% depending on

the tissue, the remainder of the RNA consisting of tRNA or small nuclear RNAs. Therefore, even if a transcript is invariant (as expressed as a percentage of mRNA), its relative abundance would still vary when considered as a percent of the total input RNA from different source tissues.

Since the majority of the RNA is rRNA, the level of rRNA remains essentially constant from sample to sample. Because 18S and 28S rRNA make up the majority of optically absorbent material at OD_{260nm}, they should make ideal invariant controls. In fact, 18S and 28S transcripts are frequently used as internal controls in northern hybridization, RNAse protection and quantitative RT-PCR assays (see ref. 8). However, the overwhelming abundance of rRNA is a major limitation to its utility as a control in DNA microarray experiments.

In US Patent 6,057,134, Ambion describes a method to perform RT-PCR™ which allows an invariant transcript of any relative abundance such as an 18S, 28S, or 5S ribosomal RNA, actin, or glyceraldehyde 3-P phosphate dehydrogenase RNA to be used as a control for any other transcript. This allows two targets of vastly different abundance to be quantified simultaneously in a multiplex RT-PCR™ reaction. Ambion uses blocked primers, or Competimers™, that compete with the unmodified primers for binding to a DNA template but cannot be used as primers for extension by a DNA polymerase. Thus, at each extension step in PCR™, a percentage of template is unavailable for amplification. By increasing the ratio of Competimers™ to primers in a PCR™ reaction, the amplification efficiency of an amplicon can be reduced so that the linear phase of accumulation of PCR™ product matches that of a less abundant target in multiplex PCR™.

For a control to be usable for microarray hybridization, the intensity of the signal should be in the same dynamic range as the cDNA under evaluation. rRNA-derived cDNA has never previously proved useful as a control for microarrays probably because it is thousands of times too abundant compared to specific cDNA.

OBJECTS OF THE INVENTION

An object of the present invention is therefore to provide an improved method for providing an internal standard for normalizing the relative intensities of signals in hybridization arrays, an improved method for normalizing *per se* and

a method of hybridizing making use of the improved normalization.

SUMMARY OF THE INVENTION

More specifically, in accordance with the present invention, there is provided an improved method for providing an internal standard for normalizing the relative intensities of signals in hybridization arrays that is based on the use of ribosomal RNA (rRNA) as this internal standard. Ribosomal RNA has been found to be particularly suitable for this purpose because its abundance, in terms of percentage of total RNA, does not vary through the cell cycle or with a particular treatment.

The method of the present invention may be summarized as follows. On a given DNA microarray, for example, an oligonucleotide specifically recognizing a sequence contained in ribosomal RNA is spotted along with the other DNA probes used to analyze gene expression, as is usual with this technique. The spots therefore essentially consist of capture probes. Ribosomal RNA, being of relatively invariant quantity in terms of percentage relative to total RNA provides a stable quantitative control to evaluate the quantity of other types of RNA. However, since it is also found in massive amounts relative to other RNAs, its level of detection by the technique must be toned down while remaining accurate. To that end, an experimentally-defined quantity of oligonucleotides carrying the same sequence as that of the oligonucleotide capture probe found on a spot of the microarray is added to the hybridization mixture so that the excess signal coming from the labelled rRNA (or from the cDNA generated from the rRNA, if cDNA hybridization is the method selected) is competed out and the signal detected for it is reduced to a range compatible with that of the signal for the other labelled RNAs.

Specifically, the present invention provides a novel method for providing an internal standard for normalizing the relative intensities of signals on a hybridization array, comprising:

adding a known quantity of an unlabelled ribosomal nucleic acid competitor probe into a hybridization buffer suitable for

the array experiment, the competitor probe characterized in that it has the same sequence as at least portion of a capture probe present in the array for immobilizing ribosomal nucleic acids thereon; and

allowing the competitor probe to compete with a ribosomal capture probe for hybridization to a suitably labelled rRNA-derived cDNA of a cDNA sample, such that a hybridization signal of labelled rRNA-derived cDNA is decreased to a suitable signal dynamic range of detection and the rRNA-derived cDNA of the sample becomes a suitable internal standard for the hybridization array.

The method of the present invention may further include:

determinating the quantity of hybridized rRNA-derived cDNA; and

comparing the quantity of hybridized rRNA-derived cDNA against standard curves to determine the quantity of cDNA in said sample.

The present invention further provides a normalization method, wherein the above steps for obtaining an internal standard are reproduced for a test sample using a first label, and for a suitably-labelled reference sample using a second label, and the quantity of hybridized rRNA-derived cDNA originating from the test sample is compared to the quantity of rRNA-derived cDNA originating from the reference sample hybridizing to the same capture probe to provide a normalization factor.

The present invention further provides a hybridization array, wherein the above steps for normalizing are reiterated and the normalization factor is used to correct a hybridization signal provided by the binding of a target cDNA of the test sample labelled with the first label to a capture probe specific to said target, which correction makes said hybridization signal directly comparable to a hybridization signal provided by the binding of the same target of the reference

sample labelled with the second label to the same capture probe specific to said target.

In a preferred embodiment, the rRNA competitor probe is present in a concentration that is about 5 to about 100 times that of the capture probe.

The rRNA-derived cDNA may be labelled by any suitable means, such as by 3' addition of phosphate, or labelling with cyanines, biotin, digoxygenin, fluorescein, a dideoxynucleotide, an amine, a thiol, an azo (N_3) group or fluorine, or any other form of label.

An array comprising a plurality of spotted cDNA capture probes for binding ribosomal nucleics, alone or in combination with the competitor ribosomal probe in a separate component are further objects of this invention. The method of the present invention is suitable for use in high-throughput screening experiments.

It may be used for any type of array experiment, including but not limited to the identification of sequences found in the open reading frame of genes coding for transcription factors, such as c-Rel, E2F-1, Egr-1, ER, NFκB p50, p53, Sp1 and YY1.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1: A summary view of the described technology. Any given pool of total cellular RNA is usually composed of 80% ribosomal RNA (rRNA) and 20% messenger RNA (mRNA) and small nuclear RNAs. mRNA (except for the histone genes) is polyadenylated while rRNA never is. Making cDNA from both types of RNA by reverse transcription is possible if using a poly dT primer for

mRNA (producing mRNA-derived cDNA, shown by solid arrows) and a specific primer for rRNA (producing rRNA-derived cDNA, shown by dashed arrows). Analysis of mRNA by microarray using the constant rRNA as a standard is made difficult by the relative overabundance of rRNA relative to mRNA; this problem is circumvented by adding to the hybridization mix a rRNA competitor probe which has the same sequence as the microarray's rRNA-cDNA capture probe (both shown as lines marked with an "r"). By sequestering the excess rRNA-derived cDNA, the competitor probe brings down the level of hybridizable and hybridized rRNA-derived cDNA to usable levels.

Figure 2: Human ribosomal DNA complete repeating unit (GB accession number #U13360). ETS: externally transcribed spacer. ITS: internally transcribed spacer. IGS: intergenic spacer. The position of a few rRNA probes is shown.

Figure 3: Illustration of spotted DNA capture probes on the slide. The slide used for the described experiment carries 12 probe blocks, identified 1 to 12. In each block there are 7 rows and 16 columns of spots. Each DNA capture probe was spotted in duplicate in an adjacent column (i.e., all odd columns correspond to a duplicate column) so there are 8 different DNA probes in a column. There are a total of 1344 spots on the slide, corresponding to duplicates of 463 different DNA capture probes and 209 negative controls (no DNA probe).

Figure 4: Cohybridization of labelled cDNA from Jurkat (reference sample: Cy3-green) and Jurkat-TPA (test sample: Cy5-red). Ratio images exported from GenePix Pro 3.0 (Axon Instruments Inc.) as JPEG (or TIFF) files are 24-bit RGB color.

Figure 5: Cohybridization of labelled cDNA from Jurkat (Cy3-green) and Jurkat-TPA (Cy5-red). Five (5) ng of rRNA competitor probe 2 was added to the hybridization mix to compete for the hybridization of the rRNA-derived cDNA to the attached rRNA cDNA capture probe 2. Ratio images exported from GenePix Pro 3.0 (Axon Instruments Inc.) as JPEG (or TIFF) files are 24-bit RGB color.

Figure 6: Cohybridization of labelled cDNA from Jurkat (Cy3-green) and Jurkat-TPA (Cy5-red). Fifty (50) ng of rRNA competitor probe 2 was added to the hybridization mix to compete for the hybridization of the rRNA-derived cDNA to the attached rRNA cDNA capture probe 2 (which has the same sequence as rRNA competitor probe 2). Ratio images exported from GenePix Pro 3.0 (Axon Instruments Inc.) as JPEG (or TIFF) files are 24-bit RGB color.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

GLOSSARY

In order to provide a clear and consistent understanding of terms used in the present description, a number of definitions are herein provided.

Array : In the context of this invention, an array is a set of different spotted DNA consisting of capture probes for target nucleic acids. Such an array is described in US Patent No. 5,700,637.

Complementary DNA (cDNA) : DNA that has been synthesized from RNA by the effect of the enzyme reverse transcriptase, converting RNA bases into their complements (A to T, U to A, G to C, C to G).

Cy3, Cy5 : Non-radioactive fluorescent dyes from Amersham Pharmacia Biotech that are widely used for labeling DNA in microarray experiments.

Feature : A feature is a spot (typically of DNA) on a slide. The collection of such features is called a microarray.

Hydridization : The process of joining two complementary strands of DNA, or one strand each of DNA and RNA, to form a double-stranded molecule.

Messenger RNA (mRNA) : RNA that is used to direct the protein synthesis that is part of gene expression. It represents but a small fraction of the total RNA found in a cell.

mRNA-derived cDNA : cDNA synthesized from a mRNA template using reverse transcriptase and a mRNA-specific primer.

Microarray-sequestered DNA or DNA capture probe: DNA (single-stranded or double-stranded) that are anchored onto the solid surface of a microarray. (See fuller description of microarrays immediately following this Glossary.)

Oligonucleotide : A short strand of single-stranded DNA, typically composed of up to 50 bases.

Pixel Intensity : The raw intensity of a pixel on a GenePix (Axon Instrument Inc.) single-wavelength or ratio image, falling in a range from 0 to 65535.

PMT : Photomultiplier tubes in scanners used to analyze array images. These array images are the end products of comparative hybridization experiments.

Ratio Image : The ratio image is an RGB (Red-Green-Blue) overlay image. In this image, wavelength #1 (635 nm) is mapped to the green channel of the RGB image, and wavelength #2 (532 nm) is mapped to the red channel. Superimposing these two images onto each other results in a third, composite image, whose color is a blend of the red and green signals.

Ratio of medians : The ratio of medians is the ratio of the background subtracted median pixel intensity at the second wavelength to the background subtracted median pixel intensity at the first wavelength.

Reference cDNA : this cDNA originates from a reference sample that is used for comparison with another one, called test cDNA obtained from a test sample. The reference cDNA serves as a control against which test cDNAs may be compared to quantify changes in the level of expression of any mRNA found in the test sample. Typically, the reference cDNA is labelled with Cy3-dCTP (green fluorescent label) when a fluorescent label is used.

RGB: Red-Green-Blue color.

Ribosomal RNA (rRNA): structural RNA found in the ribosomes. It is the most abundant form of RNA in the cell and does not vary significantly.

rRNA-cDNA probe: a probe which is designed to hybridize to the rRNA-derived cDNA found in the hybridization mixture. This probe may be the capture probe, which may have the same sequence as the rRNA competitor probe (see below) so as to compete with it for the target rRNA-derived cDNA.

rRNA competitor probe: a DNA oligonucleotide with the same sequence as part of a ribosomal RNA-cDNA sequence and capable of competing with the microarray capture probe for hybridization with a rRNA-derived cDNA. This oligonucleotide has the role of competing for the limited space available on the rRNA cDNA capture probe bound to the microarray, thus reducing the quantity of rRNA-derived cDNA which can be retained on the microarray and thus allowing the use of rRNA-derived cDNA as an « internal standard ».

rRNA-derived cDNA: cDNA synthesized from a rRNA template using reverse transcriptase and a rRNA-specific primer.

Saturation : Saturation refers to the overloading of the photodetection circuitry. Saturation can be reduced by reducing the amount of light that is reaching the PMTs, which is done by reducing the amount of incident laser light. In practice, this is accomplished by reducing the voltage of the PMT, which reduces its gain. Saturating pixels in GenePix 1.0 are shown as white pixels in the raw wavelength images.

Spotted DNA : Known DNA capture probe that is spotted onto a microarray slide and used to identify the nucleic acids present in unknown samples (test and reference). The spotted DNA could be oligonucleotide or cDNA.

Test cDNA : cDNA from a cell sample that is to be tested, in comparison with a reference sample. Typically, the test cDNA is labelled with Cy5-dCTP (red fluorescent label) when a fluorescent label is used.

Microarrays are made from a collection of purified DNAs. A drop of each type of DNA in solution is placed onto a specially-prepared glass microscope slide by an arraying machine. The arraying machine can quickly produce a regular grid of thousands of spots in a square about 2 cm on a side, small enough to fit under a standard slide cover slip. The DNA in the spots is bound to the glass

to keep it from washing off during the hybridization reaction. The choice of DNA to be used within the spots on a microarray's surface determines which genes can be detected in a comparative hybridization assay. These DNA probes could be synthetic oligonucleotides or PCR amplified DNA (hence the terms "oligo microarray" and "cDNA microarray").

The invention relates to rRNA used as an internal standard for the normalization of the fluorescence intensities in microarray analysis experiments. This can provide an estimate of relative abundance of multiple mRNAs and allow direct comparison between two RNA samples.

Use of rRNA for normalization provides a sound method of identifying differentially expressed genes between two samples because its percentage of abundance in total RNA does not vary through the cell cycle or with a particular treatment.

In order to detect the difference in gene expression between two samples on a single microarray slide, the RNA should be reverse transcribed to cDNA and labelled with two different fluorophores prior to cohybridizing both samples to the same slide and same spots simultaneously. There are several techniques that allow labeling of cDNA. Direct labeling is done by the incorporation of a fluorescent nucleotide such as, for example, Cy3-dCTP (green) or Cy5-dCTP (red) (from Amersham-Pharmacia Biotech), during the reverse transcription reaction. Other protocols may be used for labeling the cDNA following the reverse transcription reaction (indirect labeling). Alternatively, the cDNA can be used for RNA amplification involving T7 polymerase. This method relies on attaching a T7 promoter sequence to the reverse transcriptase primer used for synthesis of the first cDNA strand. After second strand cDNA synthesis, one can generate amplified RNA (aRNA) using T7 RNA polymerase and the double-stranded cDNA molecules as targets for the linear amplification. Those targets can then be labelled directly or indirectly.

In the present invention, the reverse transcriptase reaction for the cDNA labeling step involves the use of two kinds of reverse transcriptase primers in the same reaction: an oligo-dT and specific primers for rRNA (5.8S, 18S or 28S rRNA). One set of RNA to be reverse transcribed is all the polyA+ mRNA that is present in the RNA sample, the other set is the rRNA. Both sets are labelled

in the same sample with the same label. Random short primer like random hexamers or sets of specific primers could also be used as alternative methods to reverse transcribe all the polyA+ mRNA.

In a typical experiment, the reference cDNA is labelled with Cy3 and the test cDNA is prepared in the presence of Cy5. Both of these cDNA populations are hybridized to the same spotted DNA capture probes on the microscope slide. After the hybridization and washing steps, the slide is scanned at the appropriate wavelengths and an image is generated for each wavelength. In the derived ratio image, a red spot indicates that the test cDNA for this feature is more abundant than the reference cDNA which means that the test cDNA is being expressed at a level higher than the reference cDNA; a yellow spot means that there is no change in the expression level between the two populations of test and reference cDNA. In order to measure changes in gene expression numerically, image analysis software like GenePix 1.0 (Axon Instruments, Inc.) extracts the intensity of a given feature (spot) from an image and performs a number of computations on the raw data. In this kind of comparative analysis, normalization is essential to compensate for variations in RNA isolation techniques, initial quantification errors, tube to tube variation in reverse transcriptase reactions and other experimental variations. That is where the present invention intervenes : normalization is possible upon correcting the green intensity and the red intensity of the spot having the internal standard capture probe to achieve a ratio of 1. This normalization therefore leads to the obtention of a correction factor that is applied to the intensities of signals specific to each reference and test samples.

The end product of a comparative hybridization experiment is a scanned array image. Saturated pixels appear when there are more photons detected than can be processed by the photomultiplier tubes (PMT) of the scanner. This occurs when the amount of hybridized target per shot is too high. Saturated pixels cannot be used for proper measurement of the signal intensity. PMT should then be set to avoid the detection of saturated pixels. As a consequence, this reduces the signal intensity of all other spots and low levels of cDNA will not be detected.

In the present invention, the hybridization step is performed with specific amounts of free rRNA-derived cDNA (competitor probe) added into the

hybridization buffer so as to set up a competition for ribosomal cDNA of the test cDNA and of the reference cDNA (if the latter is part of the experiment) with the capture probe. For efficient competition, the competition probe should be nearly identical to the capture probe or have a high level of overlapping sequences therewith. The hybridization efficiency of the rRNA-derived cDNA with the capture probe can be predictably and reproducibly altered. Reducing the hybridization of these internal and abundant targets in microarray experiments has the effect of generating a signal intensity in the same dynamic range of detection as the less abundant targets in microarrays.

The competition is important because the control must be detected at a level similar to the test transcript. If one target is present at a significantly higher concentration than the other, the PMT (laser voltage) has to be reduced to avoid a saturated signal, with the consequence of reducing all the other signals. The ability to obtain quantitative information for low abundant mRNA will then be lost.

With the applicants' invention, the normalization factor is computed using the ratio of intensity obtained between the signal detected for the test cDNA and that of the reference cDNA. This ratio should be 1.0. For example, if the ratio is 0.8, a normalization factor of 1.25 would have to be calculated (1/0.8). The analyzed data is then corrected using this factor. If the normalization factor is greater than 2 (or less than 0.5) the slide is usually rescanned with other PMT voltage to ensure maximum data integrity.

RESULTS

The applicants used the products and protocols that are described herein, which results in proper normalization.

Figure 1 illustrates how a given sample (reference or test) is labelled and hybridized to capture probes (a plurality of specific cDNA probed spots and one internal standard probe spot). The labelled ribosomal cDNA is mixed with a competitor probe that is here identical to the capture probe.

Figure 2 illustrates the organization of the rDNA locus. The microarray was made from a collection of synthetic DNA oligonucleotides as DNA probes.

Figure 3 illustrates the positions of spotted DNA capture probes on the slide. In order to use the cDNA made from rRNA for normalisation, a DNA capture probe having a sequence that is complementary to the rRNA-derived cDNA has also been spotted on the array slide.

Table 1 shows the sequences of two DNA probes designed for that purpose. 3D-Link Activated slides from Surmodics Inc. were used according to the supplier's protocol for the covalent attachment of the 5' amino modified oligonucleotides and prehybridization treatment of the slides. On the DNA microarray used here, each spot contains approximately 0.15ng of bound DNA probe.

The cDNA for microarray analysis was prepared from RNA templates by incorporation of fluorescent-labelled deoxyribonucleotides during first strand cDNA synthesis. 10μg of total RNA extract from Jurkat and Jurkat-TPA cell lines (Geneka Biotechnology) was used. Priming of cDNA synthesis was performed using 2μg of oligo (dT). For each labeling reaction, 50 ng of 18S primer were included to allow reverse transcription of the 18S rRNA. Table 1 shows the sequences of the 18S reverse transcriptase primer. In this experiment, labelled reference cDNA from Jurkat total RNA was prepared using Cy3-dCTP while Jurkat-TPA total RNA was reverse transcribed and labelled using Cy5-dCTP (Amersham Pharmacia Biotech) to produce labelled test cDNA. Reverse transcriptase reactions were performed using the Superscript II reverse transcriptase (LifeTechnologies) enzyme according to the supplier's protocol.

For the hybridization and washing steps the following conditions were used (optimized conditions for 3D-Link Activated slides, Surmodics Inc.). Labelled cDNAs were cohybridized in 5x SSC-0.1% SDS buffer for 16 hours at 45°C. Washing was performed by incubating slides two times 15 minutes in 2x SSC-0.1% SDS at 45°C, one time 5 minutes in 0.2x SSC at room temperature and one time 5 minutes in 0.1x SSC at room temperature. Slides were dried by low speed centrifugation.

The test and reference cDNAs were analyzed through hybridization with the microarray-sequestered cDNA. In this type of experiment, if the test or

reference cDNA contains a sequence that is complementary to the DNA on a given spot, that cDNA will hybridize to the spot, where it will be detectable by virtue of its fluorescence.

Figure 4 shows a ratio image of a typical cohybridized cDNA with no internal standard according to the invention. The target cDNAs and the results are listed in Table 2 (see right column). Figures 5 and 6 show counterparts of arrays of Figure 4 but with 5 ng and 50 ng of ribosomal competitor probe, respectively, in accordance with this invention. The results are listed in Table 2, in the middle and left columns, respectively.

Saturated spots were observed for the two rRNA cDNA probes (DNA probe 1 and probe 2). The GenePix 3.0 software (Axon Instruments Inc.) was used to extract the intensity of each feature (hybridized spot) from the image. Table 2 shows the mean value of pixel intensity for each spot. To analyse feature intensity and calculate a ratio, the local background should be subtracted from the median value of the pixel. The method used by GenePix Pro 3.0 for determining the background intensity is a local background subtraction technique. A different background is therefore computed for each individual feature-indicator and the median value of the background pixel intensities are reported (Table 2).

The end product of a comparative hybridization experiment is a scanned array image. Saturated pixels appear when there are more photons detected than the photomultiplier tubes (PMT) of the scanner can process. This occurs when the amount of hybridized cDNA to the spot is too high. Saturated pixels cannot be used for proper meaurement of the signal intensity. PMT should then be set to avoid the detection of saturated pixels. As a consequence, this reduces the signal intensity of all other spots, and lower levels of cDNA will not be detected.

Because of the high abundance of the rRNA-derived cDNA relatively to the mRNA-derived cDNA, it is important to reduce its hybridization to the microarray-sequestered DNA. In this invention, the applicants compete the hybridization of the rRNA-derived cDNA to the microarray DNA capture probe by adding a defined amount of rRNA competitor probe in the hybridization buffer, said probe carrying the same sequence as the microarray-bound probe. Five (5) to 100 molar excess of competitor probe relative to the quantity of

microarray DNA capture probe is enough to obtain a rRNA-derived cDNA signal intensity in the same dynamic range of detection as the other cDNAs (i.e.; test and/or reference mRNA-derived cDNA), which are otherwise present in much lesser quantities in the reaction buffer. The amount of molar excess to be used is essentially a function of the amount of the total RNA used for the assay (for example : 0.2 to 20 µg).

In short, because of their relatively invariant expression across tissues and treatments, 18S and 28S RNA are ideal internal controls for quantitative RNA analysis by microarrays. The current invention describes how to use these rRNAs to that end by compensating, thanks to competition with specific oligos, for their overabundance relative to the mRNA of test and reference cell samples.

The overall exhaustive results of comparison of test and reference cDNAs, normalized in accordance with the method and principles of the present invention, are provided in appendix 1.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention, as defined in the appended claims.

Name	DNA sequences	Positions relative to 5' 18S sequence	Spotted position		
			Block	Column	Row
RT primer	CTTATGACCCGCACTTACTCG	5'-1667-1647-3'	-	-	-
DNA probe 1	CCCGAGCCGCCTGGATACCGCAGCTAGGAATAATGGAATA	5'-833-872-3'	8	1	5
			8	2	5
			1	11	6
			1	12	6
DNA probe 2	TCTCGATTCCGTGGGTGGTGGTGCATGGCCGTTCTTAGTT	5'-1308-1647-3'	10	1	5
			10	2	5
			3	11	6
			3	12	6

Table 1

					Hybridization with 50 ug of probe 2 as competitor					Hybridization with 5 ug of probe 2 as competitor					Hybridization without competitor				
					Ratio of median value					Ratio of median value					Ratio of median value				
					Not normalized	beta-actin	18 S			Not normalized	beta-actin	18 S			Not normalized	beta-actin	18 S		
Block	Column	Row	Gene Name	Probe name	-	1.02	-	F635 median	F532 median	-	1.20	1.11	F635 median	F532 median	-	0.56	-	F635 median	F532 median
8	1	5	18S	probe 1	1.04	1.02	undetectable	27878	26872	0.73	0.61	0.66	5617	7877	1.01	1.80	saturated	65181	65226
1	11	6	18S	probe 1	1.00	0.98	undetectable	65217	65349	0.77	0.65	0.70	50642	65367	1.01	1.80	saturated	65181	65226
1	12	6	18S	probe 1	1.00	0.98	undetectable	65217	65352	0.68	0.56	0.61	28798	42677	1.01	1.80	saturated	65160	65187
8	2	5	18S	probe 1	0.85	0.83	undetectable	21986	26060	0.79	0.66	0.71	4808	6252	1.01	1.80	saturated	65154	65211
10	1	5	18S	probe 2	0.93	0.91	undetectable	-73	33	1.19	0.99	1.07	1446	1275	1.01	1.80	saturated	65250	65274
10	2	5	18S	probe 2	1.27	1.25	undetectable	-31	10	1.24	1.03	1.12	1437	1211	1.01	1.80	saturated	65250	65283
3	12	6	18S	probe 2	1.00	0.98	undetectable	83	254	1.01	0.84	0.92	2904	2973	1.01	1.80	saturated	65157	65199
3	11	6	18S	probe 2	1.02	1.00	undetectable	122	285	0.99	0.82	0.89	2970	3112	1.01	1.80	saturated	65115	65166
5	7	6	Beta actin	actin 1	0.78	0.76	undetectable	1159	1791	0.78	0.65	0.71	2778	3771	0.66	1.18	saturated	42650	65208
5	8	6	Beta actin	actin 1	0.88	0.87	undetectable	977	1351	0.81	0.67	0.73	2813	3723	0.60	1.07	saturated	32564	54998
10	3	1	Beta actin	actin 1	0.87	0.85	undetectable	1674	2034	0.89	0.74	0.80	2114	2491	0.54	0.96	saturated	31689	59418
10	4	1	Beta actin	actin 1	0.89	0.87	undetectable	1880	2213	0.95	0.80	0.86	1958	2142	0.50	0.89	saturated	20804	42413
4	3	1	Beta actin	actin 1	0.63	0.62	undetectable	2010	3400	0.79	0.66	0.72	886	1246	0.52	0.93	saturated	5227	10326
11	14	5	Beta actin	actin 1	0.86	0.84	undetectable	1607	1981	0.85	0.70	0.76	4081	4908	0.57	1.02	saturated	5227	9416
11	13	5	Beta actin	actin 1	0.91	0.89	undetectable	1760	2021	0.82	0.68	0.74	4163	5178	0.57	1.02	saturated	4828	8663
4	4	1	Beta actin	actin 1	0.68	0.67	undetectable	1833	2880	0.84	0.70	0.76	630	861	0.47	0.85	saturated	3316	7269
6	1	1	Beta actin	actin 2	0.96	0.94	undetectable	3619	3853	1.34	1.12	1.21	8216	6179	0.61	1.10	saturated	12776	21111
3	2	1	Beta actin	actin 2	0.88	0.86	undetectable	278	603	1.13	0.94	1.02	2734	2573	0.60	1.07	saturated	11482	19359
4	2	1	Beta actin	actin 2	0.81	0.80	undetectable	1667	2185	1.07	0.89	0.97	3255	3107	0.56	1.00	saturated	9879	18018
6	2	1	Beta actin	actin 2	1.00	0.98	undetectable	3013	3092	1.29	1.07	1.16	5016	3954	0.62	1.10	saturated	8311	13731

					Hybridization with 50 ug of probe 2 as competitor					Hybridization with 5 ug of probe 2 as competitor					Hybridization without competitor				
					Ratio of median value					Ratio of median value					Ratio of median value				
Block	Column	Row	Gene Name	Probe name	Not normalized -	beta-actin 1.02	18 S -	F635 median	F532 median	Not normalized -	beta-actin 1.20	18 S 1.11	F635 median	F532 median	Not normalized -	beta-actin 0.56	18 S -	F635 median	F532 median
1	8	6	Beta actin	actin 2	0.75	0.73	undetectable	1641	2348	0.90	0.75	0.81	5528	6304	0.56	1.01	saturated	8060	14583
4	1	1	Beta actin	actin 2	0.75	0.73	undetectable	1651	2355	0.86	0.72	0.78	3905	4676	0.50	0.89	saturated	6632	13645
3	1	1	Beta actin	actin 2	0.93	0.91	undetectable	419	686	1.13	0.95	1.02	6154	5479	0.56	1.00	saturated	5885	10732
5	1	1	Beta actin	actin 2	0.87	0.86	undetectable	530	827	0.97	0.81	0.88	2991	3266	0.51	0.92	saturated	4246	8568
5	2	1	Beta actin	actin 2	0.79	0.77	undetectable	323	673	0.80	0.67	0.72	1924	2563	0.50	0.89	saturated	3917	8126
1	7	6	Beta actin	actin 2	0.76	0.75	undetectable	2157	2986	0.93	0.78	0.84	8491	9183	-0.91	-1.63	saturated	-206	-149
3	8	6	Beta actin	actin 3	1.41	1.38	undetectable	1765	1336	1.38	1.15	1.25	7582	5556	0.72	1.28	saturated	12612	17918
3	7	6	Beta actin	actin 3	1.26	1.23	undetectable	2079	1744	1.46	1.22	1.32	9368	6469	0.65	1.16	saturated	10632	16662
11	2	1	Beta actin	actin 3	1.51	1.48	undetectable	1697	1175	1.73	1.44	1.56	1674	996	0.87	1.55	saturated	9874	11511
11	1	1	Beta actin	actin 3	1.50	1.47	undetectable	1852	1299	1.83	1.53	1.66	2150	1173	0.93	1.66	saturated	8951	9743
12	2	1	Beta actin	actin 3	1.22	1.19	undetectable	572	534	1.31	1.09	1.18	4607	3517	0.66	1.18	saturated	7276	11204
12	1	1	Beta actin	actin 3	1.13	1.11	undetectable	645	651	1.28	1.07	1.16	4478	3494	0.61	1.09	saturated	7196	11985
10	2	1	Beta actin	actin 3	1.11	1.09	undetectable	980	947	1.18	0.99	1.07	1003	920	0.54	0.97	saturated	6401	12065
9	2	1	Beta actin	actin 3	1.23	1.21	undetectable	1173	1020	1.65	1.37	1.49	7356	4461	0.67	1.20	saturated	5666	8611
10	1	1	Beta actin	actin 3	0.92	0.90	undetectable	514	655	1.26	1.05	1.14	5499	4379	0.53	0.94	saturated	5565	10861
8	2	1	Beta actin	actin 3	1.28	1.25	undetectable	991	808	1.69	1.41	1.52	1957	1167	0.79	1.42	saturated	4425	5686
8	1	1	Beta actin	actin 3	1.36	1.34	undetectable	931	704	1.60	1.33	1.44	1998	1288	0.66	1.19	saturated	4266	6610
9	13	5	Beta actin	actin 3	1.28	1.25	undetectable	1379	1128	1.67	1.39	1.50	4283	2609	0.62	1.11	saturated	3873	6437
9	1	1	Beta actin	actin 3	1.43	1.40	undetectable	1330	976	1.70	1.41	1.53	8913	5248	0.70	1.26	saturated	3211	4705
9	14	5	Beta actin	actin 3	1.51	1.48	undetectable	1946	1303	1.60	1.33	1.44	2481	1579	0.62	1.10	saturated	2984	5021
2	1	1	Beta actin	actin 3	0.76	0.74	undetectable	1630	2269	1.18	0.98	1.06	986	905	0.48	0.86	saturated	2319	5083

					Hybridization with 50 ug of probe 2 as competitor					Hybridization with 5 ug of probe 2 as competitor					Hybridization without competitor				
					Ratio of median value					Ratio of median value					Ratio of median value				
Block	Column	Row	Gene Name	Probe name	Not normalized -	beta-actin 1.02	18 S -	F635 median	F532 median	Not normalized -	beta-actin 1.20	18 S 1.11	F635 median	F532 median	Not normalized -	beta-actin 0.56	18 S -	F635 median	F532 median
2	2	1	Beta actin	actin 3	0.76	0.75	undetectable	1800	2462	1.13	0.94	1.02	4407	3937	0.44	0.79	saturated	2317	5572
4	2	4	9G8 splicing	L22253_B	0.69	0.68	undetectable	361	689	0.98	0.82	0.89	777	875	0.48	0.86	saturated	1217	2852
9	14	4	A-Myb	X13294_B	2.30	2.25	undetectable	197	64	2.73	2.28	2.47	1228	429	0.84	1.50	saturated	664	877
4	8	4	ASH1	L08424_A	1.33	1.31	undetectable	587	487	1.49	1.24	1.35	1332	908	0.70	1.25	saturated	3104	4657
3	5	3	BTEB	D31716_B	3.88	3.80	undetectable	332	33	2.86	2.38	2.58	1565	510	1.18	2.10	saturated	3709	3172
3	12	5	BTF3 homologue	M90355_A	4.15	4.07	undetectable	1627	338	3.47	2.89	3.13	3749	1036	1.14	2.03	saturated	5707	5036
4	4	2	CBFA1/OSF2	AF053949_B	0.52	0.51	undetectable	-136	14	1.25	1.04	1.13	62	99	0.51	0.91	saturated	219	754
2	2	5	CDP	M74099_B	0.45	0.44	undetectable	-54	173	0.79	0.66	0.72	138	296	0.32	0.57	saturated	88	743
11	10	5	cyclin D1	AML 12	1.75	1.72	undetectable	4205	2401	1.60	1.33	1.45	11710	7312	1.03	1.84	saturated	15590	15215
6	6	4	EN2	L12700_B	2.93	2.88	undetectable	1517	476	3.61	3.01	3.26	1835	458	1.41	2.51	saturated	7429	5251
8	15	6	GAPDH	S6-1	1.37	1.35	undetectable	2104	1553	2.15	1.79	1.94	3462	1593	0.43	0.76	saturated	3832	9331
2	10	2	GTF2IP1	AF036613_B	0.49	0.48	undetectable	-106	21	0.68	0.57	0.62	-45	83	0.36	0.65	saturated	20	458
5	12	1	ZRP-1	AF000974_A	2.99	2.93	undetectable	4235	1405	3.24	2.70	2.92	12043	3689	1.61	2.88	saturated	13359	8293

TABLE 2

Appendix 1: Signal normalization using 18S RNA as an internal standard. Two microarray analyses were performed independently, each one comparing the expression of many transcription factors in Jurkat cells and in Jurkat cells treated with the phorbol ester TPA. The signals obtained in the latter case were divided by the signals obtained in the former case to get a ratio of induction by TPA in these cells. The signals were normalized using 18S RNA as a standard (see columns 3 and 4). Since 18S RNA is used as a control in both experiments and that the same type of cells were used, presumably giving very similar results, the ratio of the results obtained in each experiment should be nearing 1. That ratio is presented in column 5.

Column 1	Column 2	Column 3	Column 4	Column 5
Gene name	Accession number	Jurkat/Jurkat TPA ratio experiment 1	Jurkat/Jurkat TPA ratio experiment 2	Ratio of experiments 1 and 2
9G8 splicing factor	L22253	0.84	1.00	0.836078512
9G8 splicing factor	L22253	0.77	0.99	0.779340183
A-Myb	X66087	1.32	1.38	0.950679679
A-Myb	X66087	1.34	1.43	0.937305665
A-Myb	X13294	1.12	1.21	0.924150275
A-Myb	X13294	1.12	1.21	0.924083463
ABF-1	AF060154	0.45	0.39	1.166895465
ABF-1	AF060154	0.39	0.38	1.029207795
ABH	NM_006020	0.91	1.05	0.865303363
ABH	NM_006020	0.81	0.98	0.822950019
ABP/ZF	U82613	1.32	1.64	0.804108596
ABP/ZF	U82613	1.25	1.60	0.783304597
AF10	NM_004641	1.24	1.31	0.947593818
AF10	NM_004641	1.23	1.32	0.931357689
AIB3	AF208227	1.33	1.28	1.034779297
AIB3	NM_014071	1.09	1.25	0.870698314
AIB3	NM_014071	1.07	1.36	0.784035932
AIB3	AF208227	1.10	1.40	0.782294079
ALL-1	U04737	1.65	1.88	0.880126672
ALL-1	U04737	1.58	1.88	0.838592996
ALL-1	L04284	0.66	0.79	0.838134698
AML2	Z35278	0.44	0.51	0.858684813
AML2	Z35278	0.42	0.55	0.77112205
AML3	AF001450	1.28	1.32	0.974983445
AML3	AF001450	1.34	1.39	0.966458433
AP-2gamma	U85658	2.57	2.62	0.978390776
AP-2gamma	U85658	2.23	2.59	0.86381938
AP-4	X57435	1.21	1.23	0.984438472
AP-4	X57435	1.17	1.28	0.91144528

AP4	NM_014374	1.39	1.59	0.871879245
AP4	NM_014374	1.32	1.59	0.831996755
APBB1	NM_001164	0.95	0.97	0.984113563
APBB1	NM_001164	0.79	0.99	0.801180869
APC	M74088	1.50	1.31	1.148676257
APC	M74088	1.29	1.46	0.8859936
APECED	AB006682	1.49	1.56	0.957659838
APECED	AB006682	1.38	1.65	0.837168643
APEX	NM_001641	0.88	1.13	0.783250131
APEX	NM_001641	0.84	1.08	0.780343345
APOBEC2	NM_006789	1.15	1.12	1.031439776
APOBEC2	NM_006789	1.04	1.05	0.990111417
APPL	NM_012096	1.32	1.54	0.856820461
APPL	NM_012096	1.31	1.56	0.839878811
AR	NM_000044	1.74	2.04	0.855879355
AR	NM_000044	1.60	2.01	0.796494966
ARNT	M69238	1.25	1.42	0.880056649
ARNT	M69238	1.24	1.42	0.876705905
ARNT	Y18500	0.78	0.96	0.816130578
ASH2L2	AF056717	1.34	1.35	0.994678817
ASH2L2	AF056717	1.38	1.40	0.991252318
ATBF1	NM_006885	0.90	1.01	0.889758762
ATBF1	NM_006885	0.90	1.02	0.879456944
ATF	D90209	1.05	1.01	1.035713928
ATF	D90209	0.97	1.01	0.960323304
ATF-a	X52943	1.54	1.88	0.817277421
ATF-a	X52943	1.51	1.93	0.780957523
ATF1	NM_005171	0.84	0.91	0.927916867
ATF1	NM_005171	0.87	1.02	0.854281302
ATF6	NM_007348	1.29	1.29	1.00327664
ATF6	NM_007348	1.09	1.28	0.856533977
BACH1	NM_001186	1.49	1.31	1.137064444
BACH1	NM_001186	1.45	1.62	0.891057108
BAPX1	NM_001189	2.55	2.33	1.093826453
BAPX1	NM_001189	2.46	2.59	0.946872482
BARX2	NM_003658	1.17	1.27	0.917084438
BARX2	NM_003658	1.14	1.37	0.830998058
BCL2	NM_000633	1.43	1.65	0.866945304
BCL2	NM_000633	1.37	1.70	0.806442848
BCL3	U05822	1.11	1.26	0.877431885
BCL3	M31732	1.17	1.38	0.848343893
BCL3	M31732	1.13	1.37	0.825031918
BCL3	U05822	1.02	1.30	0.790257156
Beta-actin	X00351	1.02	1.19	0.855958172
Beta-actin	X00351	1.02	1.21	0.843968769
Beta-actin	X00351	1.01	1.21	0.837209294
Beta-actin	X00351	1.00	1.19	0.836410947
beta-catenin	X89593	2.01	2.06	0.977986591
beta-catenin	X89593	1.99	2.11	0.942592932
BF-2	X74143	1.28	1.38	0.931388014

BF-2	X74143	1.22	1.37	0.894927517
BFP/ZNF179	AB026054	1.33	1.32	1.005754548
BFP/ZNF179	AB026054	1.36	1.37	0.993222418
BIRC4	NM_001167	1.51	1.44	1.054435009
BIRC4	NM_001167	1.40	1.50	0.932289706
BMZF3	NM_005773	0.92	1.08	0.850837495
BMZF3	NM_005773	0.90	1.13	0.798215326
brahma	X72889	5.90	5.49	1.074544412
brahma	X72889	5.14	5.97	0.86166573
BRCA2	NM_000059	1.45	1.75	0.824507422
BRCA2	NM_000059	1.39	1.74	0.798236353
Brn-3B	U06233	1.48	1.37	1.078166711
Brn-3B	U06233	1.47	1.50	0.974841891
Brn-4	X82324	1.57	1.06	1.486851514
Brn-4	X82324	1.29	1.07	1.198217087
BRS3	NM_001727	2.71	2.75	0.983814035
BRS3	NM_001727	2.36	2.77	0.851828571
BTEB	D31716	4.86	4.21	1.153934489
BTEB	D31716	4.30	4.32	0.995197771
BTEB2	D14520	1.25	1.27	0.978590601
BTEB2	D14520	1.30	1.39	0.933625786
BTF3	NM_001207	1.05	1.10	0.955111894
BTF3	NM_001207	0.99	1.08	0.913787418
BTF3a	M90352	2.83	2.32	1.219855319
BTF3a	M90352	2.70	2.39	1.130461687
BTF3L1	NM_001208	1.22	1.07	1.137813523
BTF3L1	NM_001208	1.16	1.05	1.102860167
BTF3L3	M90356	1.44	1.37	1.049188317
BTF3L3	M90356	1.24	1.34	0.927268611
bZip protein B-ATF	U15460	1.07	1.14	0.9426678
bZip protein B-ATF	U15460	0.97	1.08	0.901877866
c-Ets-1	X14798	1.09	1.25	0.873492353
c-Ets-1	X14798	1.10	1.32	0.830363686
c-maf	AF055376	5.74	4.79	1.19705637
c-maf	AF055376	4.91	5.10	0.962031195
c-Rel	M11595	1.33	1.41	0.946493027
c-Rel	X75042	1.32	1.46	0.902036285
c-Rel	M11595	1.27	1.42	0.889929469
c-Rel	X75042	1.14	1.47	0.777782886
C2H2 ZNF	AF033199	1.07	1.14	0.938338671
C2H2 ZNF	AF033199	0.99	1.16	0.852890579
C2H2-type ZNF	U95991	1.19	1.01	1.173282928
C2H2-type ZNF	U95991	0.98	1.04	0.942590144
C2ORF3	NM_003203	1.46	1.22	1.196699322
C2ORF3	NM_003203	1.01	0.93	1.093811577
CBF (5)	M37197	4.06	4.25	0.956014195
CBF (5)	M37197	3.60	4.09	0.88090602
CBF1	AF098297	1.61	1.63	0.991664197
CBF1	AF098297	1.38	1.78	0.772546908
CBFA1	L40992	1.30	1.45	0.898057655

CBFA1	L40992	1.26	1.46	0.865127809
CBFA1/OSF2	AF053949	1.22	1.28	0.951727989
CBFA1/OSF2	AF053949	1.22	1.33	0.92146037
CBFA2T1	NM_004349	1.49	1.65	0.901008111
CBFA2T1	NM_004349	1.24	1.59	0.780002118
CBFB	L20298	2.33	2.74	0.851333501
CBFB	L20298	2.36	2.91	0.8088749
CDP	M74099	1.39	1.61	0.85914075
CDP	M74099	1.27	1.64	0.77621359
CEBPB	NM_005194	1.24	1.47	0.846246886
CEBPB	NM_005194	1.26	1.49	0.846246188
CEBPD	NM_005195	0.83	1.00	0.829917576
CEBPD	NM_005195	0.84	1.03	0.822579365
CEBPE	U48866	1.91	2.01	0.948532903
CEBPE	U48866	2.06	2.38	0.86669978
CEZANNE	NM_020205	2.88	2.96	0.974633442
CEZANNE	NM_020205	2.65	2.83	0.935357017
CHD1	NM_001270	1.62	1.59	1.014951939
CHD1	NM_001270	1.43	1.59	0.898362477
CHD4	NM_001273	1.54	1.70	0.909055986
CHD4	NM_001273	1.49	1.72	0.862018232
CHFR	NM_018223	4.35	4.43	0.982194772
CHFR	NM_018223	3.92	4.36	0.899117503
CHN1	NM_001822	1.42	1.53	0.927629676
CHN1	NM_001822	1.37	1.49	0.923095091
CIS4	NM_004232	1.67	1.79	0.935688257
CIS4	NM_004232	1.82	2.13	0.851569476
CITED1	NM_004143	1.10	1.30	0.850853943
CITED1	NM_004143	1.17	1.39	0.844249881
CNBP	M28372	0.67	0.54	1.233592517
CNBP	M28372	0.62	0.54	1.163359863
coactivator EBV nuclear protein 2	U22055	0.82	0.94	0.869546763
coactivator EBV nuclear protein 2	U22055	0.81	1.00	0.810099254
COPEB	NM_001300	1.14	1.29	0.885046712
COPEB	NM_001300	1.12	1.34	0.833843243
COPS5	NM_006837	2.46	2.14	1.148421053
COPS5	NM_006837	2.48	2.32	1.071355007
CP2	U01965	1.01	1.23	0.82004865
CP2	U01965	1.00	1.30	0.771414141
CR53	AF017433	1.33	1.33	0.997732351
CR53	AF017433	1.29	1.39	0.925956448
CRE-BP1	J05623	1.13	1.38	0.819277436
CRE-BP1	J05623	1.02	1.26	0.815059942
CREB	M27691	0.92	1.09	0.842697518
CREB	M27691	0.85	1.06	0.7964146
CREBBP	NM_004380	1.09	1.25	0.872661186
CREBBP	NM_004380	1.12	1.30	0.86705145
CREBPA	NM_004904	1.26	1.30	0.971711147
CREBPA	NM_004904	1.10	1.24	0.887551154

CROC4	NM_006365	1.15	1.25	0.926055212
CROC4	NM_006365	1.16	1.38	0.842320854
CRSP70	NM_004831	0.91	1.06	0.854668195
CRSP70	NM_004831	0.92	1.15	0.803384327
CRSP9	NM_004270	1.37	1.49	0.919973517
CRSP9	NM_004270	1.40	1.53	0.919262135
CSDA	NM_003651	2.00	2.09	0.956497534
CSDA	NM_003651	1.79	2.09	0.857935728
CSPG4	NM_001897	6.91	6.16	1.121744511
CSPG4	NM_001897	6.24	6.25	0.998642122
cyclin T1	AF048730	1.27	1.54	0.823279433
cyclin T1	AF048730	1.20	1.47	0.813677962
cyclin T2a	AF048731	1.50	1.54	0.973727374
cyclin T2a	AF048731	1.65	1.70	0.971786333
Daxx	AB015051	1.22	1.49	0.814149894
Daxx	AB015051	1.16	1.45	0.796739358
DB1	D28118	1.21	1.38	0.873780256
DB1	D28118	1.20	1.38	0.871224304
DDXBP1	NM_016166	1.20	1.32	0.908250709
DDXBP1	NM_016166	1.14	1.32	0.865664426
DED	AJ249940	0.85	0.90	0.947823489
DED	AJ249940	0.84	0.90	0.93599742
DEK	S89712	1.38	1.62	0.856330516
DEK	S89712	1.32	1.55	0.852478465
DFFB	NM_004402	1.36	1.40	0.968276574
DFFB	NM_004402	1.22	1.55	0.787420865
DIP1	NM_012142	1.39	1.14	1.217929208
DIP1	NM_012142	1.17	1.15	1.01617335
DLC1	NM_006094	3.06	3.29	0.931248269
DLC1	NM_006094	2.97	3.29	0.903164687
DLX3	NM_005220	1.13	1.26	0.894141987
DLX5	NM_005221	1.45	1.39	1.04166642
DLX5	NM_005221	1.25	1.61	0.775477519
DMAHP	X84813	1.10	1.29	0.851587242
DMAHP	X84813	1.08	1.31	0.825399746
DMRT1	AJ276801	1.41	1.41	1.002793104
DMRT1	AJ276801	1.43	1.48	0.961743556
DNA-binding protein	X60824	1.36	1.52	0.897844438
DNA-binding protein	X60824	1.32	1.48	0.88927803
DNASE1	NM_005223	1.21	1.25	0.964151008
DNASE1	NM_005223	0.97	1.21	0.798481304
DNASE2	NM_001375	2.98	3.43	0.867988126
DNASE2	NM_001375	2.89	3.55	0.815129956
DRA	NM_000111	1.26	1.39	0.904139999
DRA	NM_000111	1.21	1.41	0.862444488
DREAM	AJ131730	0.78	0.96	0.819901761
DREAM	AJ131730	0.76	0.98	0.770874238
E2F1	M96577	0.89	1.03	0.869321414
E2F1	M96577	0.91	1.05	0.867695906
EAR-1r	D16815	2.06	2.10	0.984212792

EAR-1r	D16815	1.88	2.21	0.850783292
EGR1	X52541	1.47	1.50	0.979883348
EGR1	X52541	1.44	1.51	0.953589751
EGR1	M17254	0.86	1.03	0.832083695
EGR1	M17254	0.87	1.05	0.827505943
EGR4	NM_001965	0.60	0.71	0.840382873
EGR4	NM_001965	0.63	0.81	0.775954581
EKLF	U65404	0.98	1.04	0.944031465
EKLF	U65404	0.96	1.03	0.935317019
ELF1	M82882	1.76	1.83	0.964878433
ELF1	M82882	1.62	1.76	0.921751518
ELF4	NM_001421	1.45	1.41	1.027947336
ELF4	NM_001421	1.36	1.37	0.991044834
ELK3	NM_005230	1.28	1.57	0.815739725
ELK3	NM_005230	1.33	1.68	0.790796088
ELL	NM_006532	0.95	1.16	0.822566492
ELL	NM_006532	0.95	1.16	0.819455294
elongation factor 1-alpha	X16869	1.35	1.50	0.8947725
elongation factor 1-alpha	X16869	1.36	1.59	0.853485168
elongation factor SIII	L34587	1.41	1.64	0.861800291
elongation factor SIII	L34587	1.49	1.82	0.820065033
elongation factor-1-delta	Z21507	0.81	0.99	0.81190776
elongation factor-1-delta	Z21507	0.78	1.00	0.782148893
EN1	L12698	1.36	1.45	0.935865444
EN1	L12698	1.23	1.47	0.836794344
EPAS1	NM_001430	1.18	1.38	0.856844874
EPAS1	NM_001430	1.15	1.46	0.783761416
ERCC2	X52222	5.72	4.80	1.193231705
ERCC2	X52222	5.33	4.73	1.127089247
ERCC3	NM_000122	1.36	1.57	0.863467286
ERCC3	NM_000122	1.30	1.60	0.812147676
ERF-2	X78992	2.14	2.41	0.889330713
ERF-2	X78992	2.26	2.55	0.883602051
ERG	NM_004449	1.62	1.42	1.142428678
ERG	NM_004449	1.49	1.50	0.996969892
ERM	X96375	4.16	4.29	0.969559654
ERM	X96375	3.27	3.55	0.921520209
ERT	AF017307	2.43	2.68	0.90894817
ERT	AF017307	2.51	2.82	0.891141057
ESRRG	NM_001438	0.95	1.13	0.839582135
ESRRG	NM_001438	0.95	1.15	0.821231854
ETR101	NM_004907	2.74	2.75	0.997375352
ETR101	NM_004907	2.49	2.80	0.887790293
Ets transcription factor ESE-2b	AF115403	1.14	1.31	0.87442124
Ets transcription factor ESE-2b	AF115403	1.11	1.43	0.77156259
Ets-1 gene	AF193068	1.21	1.38	0.874625305
Ets-1 gene	AF193068	1.22	1.40	0.868962372

Ets-like	U30174	1.40	1.23	1.131217765
Ets-like	U30174	1.49	1.35	1.098811633
Ets-like	Z49980	1.61	1.51	1.067048232
Ets-like	Z49980	1.54	1.56	0.991710772
Ets2	M30137	1.75	2.02	0.86945137
Ets2	M30137	1.78	2.11	0.844919404
ETV1	NM_004956	1.13	1.25	0.910122678
ETV1	NM_004956	1.39	1.59	0.871215971
ETV6	U45432	1.38	1.43	0.965065589
ETV6	NM_001987	0.90	1.11	0.811726255
Evi-1	S82592	2.53	2.10	1.208239627
Evi-1	S82592	2.26	2.15	1.055074375
EWSR1	NM_005243	1.01	1.28	0.789906804
EWSR1	NM_005243	1.00	1.28	0.783731221
EZH2	U61145	1.26	1.35	0.932953273
EZH2	U61145	1.27	1.39	0.907474288
FACTP140	NM_007192	1.43	1.48	0.96265369
FACTP140	NM_007192	1.41	1.48	0.954817504
Fas-binding protein Daxx	AF015956	0.90	1.08	0.833884369
Fas-binding protein Daxx	AF015956	0.89	1.09	0.81465638
FBW1A	AF129530	1.31	1.45	0.900471742
FBW1A	AF129530	1.27	1.54	0.829306514
FGD1	U11690	1.33	1.14	1.173441119
FGD1	U11690	1.21	1.23	0.990554056
FGR	NM_005248	1.33	1.58	0.839283541
FGR	NM_005248	1.27	1.60	0.790883893
FHL1	AF110763	1.56	1.77	0.88200997
FHL1	AF110763	1.45	1.76	0.822210318
FKHL7	AF048693	3.42	3.29	1.040543697
FKHL7	AF048693	3.65	3.62	1.006927826
FKHR	AF032885	2.42	2.08	1.161966778
FKHR	AF032885	2.36	2.18	1.082816723
FKHRL1P1	AF032887	1.42	1.54	0.924383924
FKHRL1P1	AF032887	1.46	1.60	0.912174436
FLI_CDNA	AL360183	1.33	1.28	1.036167415
FLI_CDNA	AL360183	1.37	1.37	0.996443864
FLJ10173	NM_018014	1.04	1.04	0.999229429
FLJ10173	NM_018014	1.01	1.01	0.996944727
FLJ10251	NM_018039	1.31	1.43	0.911977997
FLJ10251	NM_018039	1.31	1.46	0.897214657
FLJ10339	NM_018063	1.62	1.87	0.866263178
FLJ10339	NM_018063	1.53	1.86	0.822236451
FLJ10469	NM_018102	0.94	1.09	0.865336872
FLJ10469	NM_018102	0.94	1.09	0.865236102
FLJ10688	AK001550	0.97	1.11	0.881574929
FLJ10688	AK001550	0.95	1.19	0.802514491
FLJ10891	NM_018260	1.22	1.31	0.928051813
FLJ10891	NM_018260	1.15	1.38	0.83802715
FLJ10909	AK001771	2.36	2.38	0.988865574

FLJ10909	AK001771	2.19	2.39	0.917728349
FLJ11015	NM_018300	1.10	1.19	0.922727928
FLJ11015	NM_018300	0.99	1.17	0.845365497
FLJ11137	NM_018337	1.43	1.64	0.875337744
FLJ11137	NM_018337	1.33	1.60	0.831187459
FLJ11340	AK002202	3.74	3.96	0.944037815
FLJ11340	AK002202	3.72	4.02	0.925252175
FLJ11344	AK002206	1.11	1.24	0.900786005
FLJ11344	AK002206	1.22	1.39	0.879708376
FLJ11688	AK021750	1.31	1.41	0.925531252
FLJ11688	AK021750	1.35	1.50	0.901037884
FLJ12606	AK022668	1.11	1.15	0.965529216
FLJ12606	AK022668	0.96	1.10	0.876202729
FLJ12628	AK022690	1.30	1.38	0.938935506
FLJ12628	AK022690	1.25	1.36	0.925116959
FLJ12644	AK000909	0.98	1.09	0.901825689
FLJ12644	AK000909	1.02	1.16	0.874104763
FLJ13479	AK023541	1.12	1.35	0.830838509
FLJ13479	AK023541	1.05	1.27	0.825925564
FLJ20337	NM_017772	1.55	1.60	0.969110576
FLJ20337	NM_017772	1.60	1.66	0.966477023
FLJ20428	AK000435	1.00	1.13	0.88699187
FLJ20428	AK000435	1.03	1.16	0.883146291
FLJ20438	ak000445	2.61	2.97	0.876697181
FLJ20438	ak000445	2.41	2.99	0.807812353
FLJ22332	AK025985	1.37	1.67	0.823105199
FLJ22332	AK025985	1.22	1.52	0.80219778
FLJ22973	AK026626	0.93	1.11	0.841359026
FLJ22973	AK026626	0.94	1.14	0.825377156
FOG2	NM_012082	1.03	1.10	0.930301277
FOG2	NM_012082	1.11	1.24	0.901732208
FOSL2	NM_005253	1.42	1.73	0.818161857
FOSL2	NM_005253	1.40	1.80	0.775807396
FOXD2	NM_004474	1.36	1.49	0.918399567
FOXD2	NM_004474	1.35	1.48	0.912187342
FOXD3	NM_012183	1.67	1.55	1.072311149
FOXD3	NM_012183	1.55	1.63	0.952188792
FOXO3A	NM_001455	0.87	1.10	0.789948212
FOXO3A	NM_001455	0.85	1.09	0.780082817
FRA-1	X16707	1.19	1.22	0.975373174
FRA-1	X16707	1.15	1.25	0.920368654
FREAC1	U13219	1.33	1.44	0.920850002
FREAC1	U13219	1.33	1.47	0.900355759
FREAC10	AF042831	1.37	1.53	0.895510594
FREAC10	AF042831	1.29	1.49	0.862685753
FREAC6	L13203	0.68	0.76	0.894745854
FREAC6	L13203	0.65	0.75	0.865206105
FREAC7	U13225	0.82	0.70	1.159351607
FREAC7	U13225	0.70	0.72	0.971169803
frpHE	AF026692	1.02	1.11	0.917414227

frpHE	AF026692	0.99	1.17	0.852068204
GABPB1	NM_005254	1.74	1.77	0.98532103
GABPB1	NM_005254	1.74	1.82	0.956282084
GADD 153	s40706	1.28	1.47	0.871741003
GADD 153	s40706	1.09	1.42	0.76973024
GAPDH	M33197	0.58	0.61	0.949162972
GAPDH	M33197	0.56	0.59	0.947048611
GCMA	NM_003643	1.20	1.32	0.908325507
GCMA	NM_003643	1.15	1.32	0.870108289
GCN5L1	NM_001487	0.80	0.93	0.856784201
GCN5L1	NM_001487	0.73	0.90	0.820087548
GIOT-1	AB021641	1.29	1.45	0.884372648
GIOT-1	AB021641	1.22	1.50	0.812297818
GIOT-2	NM_016264	0.93	1.07	0.868101488
GIOT-2	NM_016264	0.91	1.10	0.82720992
GIOT-3	NM_016265	0.87	0.97	0.893216374
GIOT-3	NM_016265	0.86	0.97	0.884789805
GIOT-4	NM_016266	1.73	2.15	0.806073313
GIOT-4	NM_016266	1.78	2.27	0.783305867
GLI	X07384	1.34	1.32	1.019171414
GLI	X07384	1.28	1.34	0.958829722
GLI3	M57609	2.18	1.98	1.098071683
GLI3	M57609	1.95	2.06	0.944192578
GPX5	NM_001509	0.94	1.08	0.865100605
GPX5	NM_001509	1.37	1.62	0.847040407
GRLF1	NM_004491	0.79	0.87	0.906709069
GRLF1	NM_004491	0.71	0.80	0.885942625
GTF2B	NM_001514	2.16	2.30	0.937394785
GTF2B	NM_001514	1.95	2.44	0.799673306
GTF2E1	NM_005513	0.76	0.98	0.784112092
GTF2E1	NM_005513	0.74	0.96	0.769972038
GTF2I	NM_001518	2.68	2.80	0.958900201
GTF2I	NM_001518	2.58	2.96	0.869928806
GTF2IP1	AF036613	0.95	0.70	1.359169172
GTF2IP1	AF036613	0.84	0.84	0.988769754
GTF3A	NM_002097	1.49	1.59	0.932083753
GTF3A	NM_002097	1.58	1.70	0.931723008
GTF3C1	NM_001520	2.07	2.25	0.919747554
GTF3C1	NM_001520	1.99	2.34	0.847308047
GTF3C2	NM_001521	1.31	1.28	1.027107124
GTF3C2	NM_001521	1.22	1.29	0.943844023
GTF3C3	NM_012086	1.64	1.64	0.996581398
GTF3C3	NM_012086	1.52	1.67	0.907893639
GTF3C4	NM_012204	1.11	1.28	0.860437792
GTF3C4	NM_012204	1.13	1.33	0.851773956
GTP	AF054183	1.98	2.25	0.880760132
GTP	AF054183	1.86	2.27	0.818437867
H1F3	M60746	1.08	1.27	0.853497342
H1F3	M60746	1.10	1.33	0.824710104
H2AFX	X14850	1.24	1.33	0.934617922

H2AFX	X14850	1.19	1.40	0.849848259
H4	X67081	0.83	0.97	0.859373264
H4	X67081	0.84	1.00	0.842811776
hairless	AF039196	1.39	1.46	0.951801096
hairless	AF039196	1.37	1.53	0.896272718
HAP2	M59079	1.59	1.49	1.062457371
HAP2	M59079	1.33	1.71	0.780793131
HAT1	NM_003642	1.05	0.86	1.223229142
HAT1	NM_003642	1.06	1.04	1.026464835
HB16	M31630	0.97	1.09	0.894291244
HB16	M31630	1.01	1.26	0.797052293
HB9	U07663	2.64	2.61	1.013508831
HB9	U07664	0.92	1.03	0.895489189
HBOA	NM_007067	1.27	1.37	0.929935594
HBOA	NM_007067	1.23	1.35	0.912294782
HCF-2	AF117210	1.43	1.56	0.918694023
HCF-2	AF117210	1.43	1.61	0.888145397
HD-ZNF1	NM_004876	1.11	1.22	0.910541692
HD-ZNF1	NM_004876	1.05	1.19	0.884372648
HDAC1	NM_004964	0.83	0.97	0.851140233
HDAC1	NM_004964	0.82	0.97	0.844737874
HDAC4	NM_006037	2.76	2.40	1.153229661
HDAC4	NM_006037	1.64	1.99	0.825094678
HEB	M83233	0.75	0.89	0.83812814
HEB	M83233	0.73	0.90	0.814864061
HEN1	M96739	1.51	1.61	0.937658625
HEN1	M96739	1.49	1.69	0.883530062
HERP1	AF232238	1.64	1.78	0.918811847
HERP1	AF232238	1.48	1.69	0.873182906
HERP2	AF232239	0.88	0.97	0.913791819
HERP2	AF232239	0.82	1.01	0.814129508
HES4	AB048791	1.12	1.24	0.906421263
HES4	AB048791	1.17	1.31	0.892326717
HGS	NM_004712	1.13	1.22	0.925941974
HGS	NM_004712	1.08	1.23	0.884627755
HIC1	NM_006497	1.01	1.19	0.84718439
HIC1	NM_006497	0.94	1.20	0.789513268
HIVEP1	NM_002114	1.24	1.14	1.08520656
HIVEP1	NM_002114	1.03	1.16	0.893216374
HIVEP2	NM_006734	2.86	2.87	0.99372865
HKE4	NM_006979	1.51	1.70	0.89115193
HKE4	NM_006979	1.35	1.66	0.814320291
HLF	M95585	1.28	1.32	0.971118298
HLF	M95586	1.15	1.26	0.910803018
HMG-1	D63874	1.27	1.25	1.015741343
HMG-1	D63874	1.23	1.22	1.008346304
HMG-2	X62534	1.70	1.82	0.938295788
HMG-2	X62534	1.55	1.76	0.878616998
HMG17	NM_005517	0.99	1.14	0.868604212
HMG17	NM_005517	0.97	1.15	0.841273347

HMGIY	NM_002131	0.92	1.04	0.886466628
HMGIY	NM_002131	0.93	1.13	0.824826257
HNF-1A	M57732	1.03	1.19	0.868596298
HNF-1A	M57732	1.07	1.25	0.861349263
HNF-1B	X71346	2.40	2.21	1.087117438
HNF-1B	X71346	2.25	2.18	1.030922798
HNF-3gamma	L12141	1.46	1.53	0.956635501
HNF-3gamma	L12141	1.40	1.54	0.90844598
HNF-4alpha3	U72967	2.92	3.06	0.953909282
HNF-4alpha3	U72967	2.76	3.16	0.871764387
HNF-6alpha	AF035580	1.20	1.00	1.202677165
HNF-6alpha	AF035580	1.02	1.07	0.954515537
HNF3A	NM_004496	1.35	1.39	0.968770391
HNF3A	NM_004496	1.30	1.39	0.934312714
HOX	L11239	1.29	1.55	0.831459424
HOX	L11239	1.22	1.56	0.784287548
HOX11	s38742	0.82	0.97	0.846268344
HOX11	s38742	0.89	1.06	0.840219605
HOX11L2	AJ223798	5.90	5.44	1.08601856
HOX11L2	AJ223798	5.29	5.47	0.967027069
HOXA-9	U81511	2.28	2.06	1.107860869
HOXA-9	U81511	2.06	2.02	1.019494694
HOXA1	S79910	1.47	1.44	1.023612925
HOXA1	S79910	1.22	1.31	0.930731462
HOXA11	AF071164	1.23	1.36	0.902672948
HOXA11	AF071164	1.28	1.48	0.86247018
HOXA13	NM_000522	7.13	5.19	1.375914112
HOXA13	NM_000522	3.90	4.45	0.876388041
HOXA4	U56105	1.20	1.41	0.854164123
HOXA4	U56105	1.19	1.46	0.814779811
HOXA7	NM_006896	1.14	1.20	0.952764133
HOXA7	NM_006896	1.09	1.21	0.899003953
HOXB1	X16666	1.59	1.81	0.877682176
HOXB1	X16666	1.62	2.00	0.80887332
HOXB2	X78978	1.84	1.60	1.145917
HOXB2	X78978	1.64	1.72	0.957991608
HOXB2	X16665	1.39	1.54	0.905368978
HOXB2	X16665	1.42	1.59	0.895429132
HOXB3	X16667	1.92	1.73	1.107588304
HOXB3	X16667	1.87	1.84	1.015740013
HOXB4	AF005652	1.16	1.27	0.911652213
HOXB4	AF005652	1.09	1.24	0.880915725
HOXB5	M92299	1.18	1.38	0.854344138
HOXB5	M92299	1.20	1.49	0.803737757
HOXB7	M16937	0.95	1.22	0.778800068
HOXB7	M16937	0.97	1.24	0.778387715
HOXC10	AF255675	1.16	1.28	0.905053085
HOXC10	X99685	1.12	1.27	0.881270065
HOXC10	AF255675	1.13	1.31	0.858450467
HOXC10	X99685	1.10	1.33	0.82796661

HOXC6	M16938	1.26	1.49	0.844466889
HOXC6	M16938	1.16	1.46	0.800039127
HOXC8	X99681	1.12	1.30	0.860768554
HOXC8	X99681	0.97	1.24	0.783209726
HOXD3	NM_006898	1.51	1.62	0.92856985
HOXD3	NM_006898	1.47	1.61	0.918716026
HOXD4	X04706	1.24	1.40	0.886519344
HOXD4	X67079	1.56	1.78	0.877418885
HOXD4	X67079	1.54	1.86	0.826005297
HOXD4	X04706	1.22	1.52	0.804048475
HPX42B	NM_014468	1.02	1.04	0.980963071
HPX42B	NM_014468	0.91	1.00	0.913143774
hRev	X72631	1.25	1.35	0.929674185
hRev	X72631	1.28	1.42	0.902255362
HS747E2A	NM_015370	1.07	1.12	0.959032318
HS747E2A	NM_015370	1.02	1.17	0.873166624
HSA275986	NM_018403	1.80	1.66	1.081002809
HSA275986	NM_018403	1.61	1.81	0.888060724
HSBP1	AF068754	2.24	2.62	0.853507954
HSBP1	AF068754	2.27	2.83	0.801085361
HSET	D14678	0.47	0.56	0.84140568
HSET	D14678	0.46	0.59	0.779570541
HSF2BP	NM_007031	2.36	2.61	0.904409562
HSF2BP	NM_007031	2.24	2.57	0.86866997
HSGT1	NM_007265	1.14	1.17	0.973056944
HSGT1	NM_007265	1.12	1.27	0.878498082
hSIM2	D85922	2.71	2.85	0.952407887
hSIM2	D85922	2.65	2.91	0.910509622
Hsp90	X07270	0.92	1.11	0.82588322
Hsp90	X15183	2.01	2.48	0.812100632
hTFIIS.h	AJ223473	0.99	1.13	0.878742961
hTFIIS.h	AJ223473	0.98	1.14	0.856298131
HUNKI	Y12059	1.59	1.62	0.976707993
HUNKI	Y12059	1.33	1.50	0.884627755
HZF2	X78925	1.12	1.19	0.948487222
HZF2	X78925	1.08	1.19	0.908973223
HZF3	X78926	1.28	1.39	0.920945575
HZF3	X78926	1.10	1.31	0.838730175
HZF8	X78931	1.56	1.52	1.022134201
HZF8	X78931	1.40	1.56	0.896953681
HZF9	X78932	1.14	1.24	0.918602524
HZF9	X78932	1.11	1.30	0.857126824
Id1	NM_002165	1.24	1.23	1.00902126
Id1	NM_002165	1.13	1.41	0.80522294
Id3	A17548	1.38	1.31	1.055781754
Id3	X69111	1.27	1.28	0.990641606
Id4	Y07958	1.15	1.26	0.913664616
Id4	Y07958	1.09	1.32	0.830113526
INsAF	s73205	1.84	2.05	0.898920183
INsAF	s73205	1.85	2.13	0.871765981

intergenic region HOXB7-HOXB6	U15407	2.30	2.60	0.88468389
intergenic region HOXB7-HOXB6	U15407	2.04	2.59	0.785453268
IQGAP2	NM_006633	1.12	1.12	0.998484582
IQGAP2	NM_006633	0.94	1.12	0.840859025
IRF-1	X14454	2.41	2.57	0.938218115
IRF-1	X14454	2.39	2.58	0.925343204
IRF2	NM_002199	3.34	2.85	1.173965009
IRF2	NM_002199	2.94	2.56	1.14907375
IRF4	U52682	1.32	1.28	1.029933166
IRF4	U52682	1.37	1.43	0.959410817
IRF5	NM_002200	1.37	1.51	0.904052621
IRF5	NM_002200	1.36	1.59	0.858607001
IRF6	NM_006147	1.29	1.58	0.813425333
IRF6	NM_006147	1.18	1.50	0.789190299
IRF7	U53830	1.84	1.44	1.27973546
IRF7	NM_004029	1.32	1.21	1.084000454
Irx-4	NM_016358	1.19	1.15	1.029933166
Irx-4	NM_016358	1.17	1.22	0.956334448
IsGF-3gamma	M87503	1.42	1.55	0.915149715
IsGF-3gamma	M87503	1.39	1.56	0.887975373
Jun-D	X56681	2.38	2.25	1.056280294
Jun-D	X56681	2.04	2.18	0.933938896
JunB	X51345	1.02	1.14	0.892190868
JunB	X51345	0.98	1.14	0.855272625
K-ALPHA-1	NM_006082	0.83	0.96	0.86884485
K-ALPHA-1	NM_006082	0.83	0.97	0.859281424
KF1	NM_005667	0.93	1.05	0.890983333
KF1	NM_005667	0.91	1.06	0.864474263
KIAA0048	D28588	1.17	1.24	0.943988673
KIAA0048	D28588	1.19	1.30	0.918453567
KIAA0065	D31763	2.61	2.47	1.058679492
KIAA0065	D31763	2.53	2.52	1.005681703
KIAA0071	NM_015156	2.49	2.21	1.124047572
KIAA0071	NM_015156	2.30	2.27	1.015956269
KIAA0130	NM_014815	1.35	1.36	0.9886418
KIAA0130	NM_014815	1.17	1.34	0.869733568
KIAA0161	D79983	1.43	1.66	0.85937708
KIAA0161	D79983	1.42	1.69	0.837823111
KIAA0211	D86966	1.41	1.67	0.846204986
KIAA0211	D86966	1.37	1.73	0.79442123
KIAA0222	D86975	2.22	2.40	0.925360475
KIAA0222	D86975	2.02	2.43	0.82835128
KIAA0244	NM_015153	1.54	1.39	1.1095751
KIAA0244	NM_015153	1.45	1.36	1.067040755
KIAA0314	AB002312	2.38	2.57	0.927343337
KIAA0314	AB002312	2.33	2.65	0.876030662
KIAA0333	AB002331	1.05	1.22	0.861487483
KIAA0333	AB002331	1.07	1.25	0.854015656
KIAA0352	NM_014830	2.88	3.18	0.9057295

KIAA0352	NM_014830	2.37	2.80	0.8492877
KIAA0395	AB007855	1.56	1.77	0.879373168
KIAA0395	AB007855	1.42	1.77	0.801179995
KIAA0426	NM_014724	1.17	1.17	0.995781911
KIAA0426	NM_014724	1.06	1.23	0.866553199
KIAA0478	AB007947	2.27	2.38	0.954072874
KIAA0478	AB007947	2.25	2.62	0.857934327
KIAA0569	NM_014795	1.66	1.65	1.011174941
KIAA0569	NM_014795	1.39	1.76	0.78836631
KIAA0595	AB011167	1.90	1.85	1.026787356
KIAA0595	AB011167	1.71	2.19	0.782500333
KIAA0600	AB011172	1.90	1.34	1.413460448
KIAA0600	AB011172	2.18	1.58	1.381300612
KIAA0929	AB023146	1.54	1.62	0.949493335
KIAA0929	AB023146	1.55	1.63	0.949132006
KIAA1015	AB023232	2.58	2.62	0.982939758
KIAA1015	AB023232	2.17	2.68	0.811021231
KIAA1259	AB033085	0.85	1.04	0.817749165
KIAA1259	AB033085	0.91	1.18	0.771007682
KIAA1442	AB037863	2.14	2.34	0.914709549
KIAA1442	AB037863	2.15	2.39	0.898110711
KIAA1528	AB040961	6.42	6.40	1.003589265
KIAA1528	AB040961	6.67	6.98	0.955545485
KIAA1741	AW081989	1.58	1.79	0.882769399
KIAA1741	AW081989	1.68	1.99	0.846731464
KID	D38751	1.54	1.48	1.042612741
KID	D38751	1.45	1.52	0.95955196
KLF13	NM_015995	1.04	1.28	0.816419879
KLF13	NM_015995	0.91	1.14	0.796485569
KNSL4	AB017335	1.22	1.41	0.866676983
KNSL4	AB017335	1.19	1.45	0.818446687
Kox1	X52332	1.02	1.16	0.880125266
Kox1	X52332	0.98	1.24	0.789133958
Kox23	X52354	0.91	1.08	0.842330108
Kox23	X52354	0.90	1.08	0.832659332
Kox26	X52357	1.00	1.19	0.83622347
Kox26	X52357	0.99	1.26	0.785398373
Kox29	X52360	0.96	1.07	0.90087877
Kox29	X52360	0.98	1.09	0.897521031
Kox30	X52361	1.58	1.72	0.918425379
Kox30	X52361	1.38	1.53	0.902401118
KRAB	M67508	1.56	1.63	0.955633904
KRAB	M67508	1.47	1.60	0.922478172
Kruppel-type ZNF	AJ245587	2.04	2.40	0.851750841
Kruppel-type ZNF	AJ245587	1.79	2.14	0.836843037
KUP	X16576	0.96	1.15	0.839112982
KUP	X16576	0.92	1.13	0.816714046
L-Myc-1(long form)	X07262	1.05	1.20	0.876584744
L-Myc-1(long form)	X07262	1.01	1.23	0.826416004
LAF4	NM_002285	0.67	0.83	0.815483937

LAF4	NM_002285	0.65	0.84	0.784014372
LBR	NM_002296	1.25	1.30	0.966371608
LBR	NM_002296	1.23	1.38	0.891519857
LD5-1	U88080	1.15	1.38	0.82971758
LD5-1	U88080	1.11	1.41	0.790825308
LDOC1	NM_012317	1.33	1.41	0.946393907
LDOC1	NM_012317	1.28	1.42	0.897325005
LEF-1	AF203908	1.27	1.37	0.928294795
LEF-1	AF203908	1.16	1.44	0.810978586
lens epithelium-derived GF	AF063020	1.24	1.42	0.870186854
lens epithelium-derived GF	AF063020	1.13	1.39	0.81400662
leucine zipper	AF056184	2.24	2.72	0.824441293
leucine zipper	AF056184	2.47	3.10	0.796652442
leucine zipper kinase AZK	AF251441	2.80	3.31	0.846204986
leucine zipper kinase AZK	AF251441	2.71	3.35	0.808081689
LHX2	NM_004789	1.42	1.48	0.953866869
LHX2	NM_004789	1.33	1.52	0.87550605
LHX6	NM_014368	1.31	1.42	0.921284172
LHX6	NM_014368	1.28	1.42	0.905610681
LIM	AF061258	1.13	1.44	0.78655152
LIM	AF061258	1.09	1.41	0.773071315
LIM domain only 1 (rhombotin 1)	M26682	1.39	1.44	0.966564434
LIM domain only 1 (rhombotin 1)	M26682	1.32	1.49	0.883805842
LIM protein MLP	U49837	0.96	1.03	0.937706079
LIM protein MLP	U49837	0.95	1.14	0.82868354
LIM1	U14755	1.17	1.23	0.952256263
LIM1	U14755	1.01	1.27	0.798369687
LIMK	D26309	2.92	3.03	0.964180024
LIMK-2	D45906	1.60	1.66	0.965944664
LIMK-2	D45906	1.63	1.73	0.945399728
LMO4	U24576	0.85	0.84	1.007125772
LMO4	U24576	0.85	0.88	0.960803963
LOC51043	NM_015872	0.86	0.91	0.949928525
LOC51043	NM_015872	0.96	1.02	0.943797482
LOC51131	NM_016119	1.08	1.04	1.041898041
LOC51131	NM_016119	1.01	1.03	0.974830053
LOC51193	NM_016331	1.18	1.40	0.846337164
LOC51193	NM_016331	1.26	1.54	0.817829826
LOC51591	NM_015905	5.44	4.01	1.354983586
LOC51591	NM_015905	5.77	4.26	1.353823958
LOC51717	NM_016285	1.43	1.55	0.919576048
LOC51717	NM_016285	1.32	1.54	0.856030646
LOC55862	NM_018479	3.18	3.29	0.96566812
LOC55862	NM_018479	2.90	3.29	0.882904561
LOC56899	AF164792	1.35	1.46	0.923685155
LOC56899	AF164792	1.24	1.47	0.843151755
LyF-1	U40462	1.17	1.33	0.881798663

LyF-1	U40462	1.04	1.28	0.809448886
LZLP	NM_013344	1.63	1.78	0.914937922
LZLP	NM_013344	1.50	1.67	0.897409878
MADH4	NM_005359	1.48	1.23	1.202041185
MADH4	NM_005359	1.27	1.13	1.118588098
MADH5	NM_005903	1.19	1.37	0.867598314
MADH5	NM_005903	1.20	1.38	0.864484722
MAF	NM_005360	0.82	0.83	0.983383327
MAF	NM_005360	0.74	0.92	0.79706277
MAFG	NM_002359	1.33	1.60	0.833961234
MAFG	NM_002359	1.37	1.65	0.833526497
MAP4	NM_002375	3.80	4.62	0.824293011
MAP4	NM_002375	3.69	4.71	0.78417244
MAPK8	NM_002750	0.88	1.00	0.88152506
MAPK8	NM_002750	0.88	1.02	0.860049569
MAZ	M94046	1.21	1.47	0.819442731
MAZ	M94046	1.19	1.48	0.804052549
MB67	Z30425	1.08	1.02	1.060408157
MB67	Z30425	0.99	1.08	0.915952791
MCG4	NM_006782	1.15	1.31	0.87362439
MCG4	NM_006782	1.15	1.34	0.857557298
MEF2A	U49020	1.18	1.29	0.917750293
MEF2A	U49020	1.08	1.27	0.851735738
MEF2B	NM_005919	1.02	1.07	0.950137026
MEF2B	NM_005919	0.95	1.04	0.910069513
MEF2D	NM_005920	1.39	1.33	1.043108425
MEF2D	NM_005920	1.20	1.44	0.837034123
metallopanstimulin	U85979	1.98	2.01	0.985678226
metallopanstimulin	U85979	1.94	2.20	0.882570172
MHox (K-2)	M95929	1.07	1.17	0.914292266
MHox (K-2)	M95929	0.95	1.17	0.810474232
Mi	Z29678	1.71	1.66	1.030471845
Mi	Z29678	1.76	1.79	0.986205176
MITF	AF034755	1.23	1.24	0.99130983
MITF	AF034755	1.32	1.50	0.883057308
Miz-1	Y09723	1.01	1.15	0.876000186
Miz-1	Y09723	0.93	1.14	0.814161592
MLH3	NM_005784	0.54	0.63	0.855999025
MLH3	NM_005784	0.62	0.78	0.801334083
MLX	AF203978	1.41	1.49	0.949042398
MLX	AF203978	1.36	1.48	0.923306997
Mog	U64564	1.32	1.37	0.960484338
Mog	U64564	1.27	1.39	0.915925265
MRG1	AF109161	3.76	4.37	0.860312626
MRG1	AF109161	3.73	4.50	0.827783082
MTERF	NM_006980	1.51	1.80	0.838119573
MTERF	NM_006980	1.35	1.70	0.789625228
MTF-1	AJ251881	2.11	2.39	0.881959401
MTF-1	AJ251881	1.95	2.39	0.815353763
mtTF1	X64269	1.47	1.59	0.925536704

mtTF1	X64269	1.44	1.57	0.914838473
MXI1	NM_005962	1.16	1.29	0.898657286
MXI1	NM_005962	1.16	1.36	0.857867078
MYBBP1A	AF147709	2.29	1.77	1.292847997
MYBBP1A	AF147709	1.85	1.75	1.054649057
MYCBP	NM_012333	3.73	3.58	1.040887845
MYCBP	NM_012333	3.47	3.48	0.997884909
MYCL2	NM_005377	2.12	2.03	1.044677307
MYCL2	NM_005377	2.04	2.00	1.018897998
MYCLK1	M64786	1.43	1.73	0.828883125
MYCLK1	M64786	1.49	1.80	0.826354974
MYT2	NM_003871	4.01	4.17	0.962205771
MYT2	NM_003871	4.04	4.42	0.915182881
N-CoR	AF044209	1.33	1.29	1.027153581
N-CoR	AF044209	1.25	1.29	0.969389141
N-Oct-3	Z11933	3.50	3.17	1.103689021
N-Oct-3	Z11933	2.91	3.05	0.955346496
N143	AJ002572	3.89	3.16	1.232431216
N143	AJ002572	2.82	3.41	0.828068155
NACA	NM_005594	1.34	1.26	1.061449635
NACA	NM_005594	1.22	1.36	0.899257451
NAGA	NM_000262	2.23	2.55	0.873072079
NAGA	NM_000262	2.02	2.54	0.795967326
NCOA1	NM_003743	1.34	1.43	0.939022342
NCOA1	NM_003743	1.36	1.45	0.932646647
NCOA3	NM_006534	2.14	2.15	0.995002762
NCOA3	NM_006534	1.97	2.05	0.959254041
NCYM	NM_006316	1.18	1.11	1.067219564
NCYM	NM_006316	1.07	1.16	0.917384574
NDUFA6	NM_002490	0.80	0.82	0.969899497
NDUFA6	NM_002490	0.71	0.92	0.772339515
Negative control	Negative control	1.29	1.11	1.161392449
Negative control	Negative control	5.43	5.29	1.027043989
NEUROD2	U58681	1.14	1.28	0.889551897
NEUROD2	U58681	1.02	1.28	0.795592113
NEUROG1	U63842	1.39	1.71	0.812574039
NEUROG1	U63842	1.29	1.63	0.795487149
NF-1X	U07811	0.99	0.82	1.215806558
NF-1X	U07811	0.64	0.82	0.782275487
NFAT1	U43341	2.28	2.65	0.861852199
NFAT1	U43341	2.30	2.80	0.819721245
NFATC1	NM_006162	1.21	1.27	0.956885723
NFATC1	NM_006162	1.20	1.33	0.906442678
NFATX	U14510	1.09	1.35	0.8066644
NFATX	U14510	0.99	1.24	0.798995238
NFIL3	NM_005384	3.33	3.43	0.969982487
NFIL3	NM_005384	3.22	3.36	0.957589194
NFKB1	M58603	2.44	2.68	0.910234175
NFKB1	M55643	1.23	1.37	0.894069494
NFKB2	U09609	1.09	1.21	0.899003953

NFKB2	U09609	1.04	1.28	0.815426014
NFKBIB	NM_002503	0.66	0.74	0.891632657
NFKBIB	NM_002503	0.61	0.73	0.835589511
NFKBIE	NM_004556	1.34	1.34	0.995844935
NFKBIE	NM_004556	1.30	1.37	0.951450999
NFkBp105	M55643	0.82	0.80	1.028950235
NFkBp105	M55643	0.78	0.88	0.882630106
ngn3	AJ133776	1.04	1.14	0.911675496
ngn3	AJ133776	1.01	1.15	0.877939013
NME2	NM_002512	1.08	1.28	0.849242645
NME2	NM_002512	0.99	1.21	0.819907039
Nmi	U32849	1.50	1.65	0.908824603
Nmi	U32849	1.46	1.67	0.874987469
NOD1	AF149774	0.88	0.97	0.913819737
NOD1	AF149774	0.80	0.97	0.829329103
NOT3	NM_014516	1.10	1.05	1.043010425
NOT3	NM_014516	1.01	1.32	0.770565768
NP220	D83032	1.59	1.80	0.886060234
NP220	D83032	1.50	1.74	0.861556367
NPAS1	NM_002517	2.55	3.06	0.832115639
NPAS1	NM_002517	2.53	3.18	0.795687598
NR0B1	NM_000475	0.89	0.90	0.985394227
NR0B1	NM_000475	0.84	1.02	0.822398708
NR2F6	NM_005234	1.11	1.26	0.878406569
NR2F6	NM_005234	1.03	1.23	0.843593242
NR3C1	NM_000176	1.45	1.63	0.884627755
NR3C1	NM_000176	1.37	1.57	0.872392013
NR4A2	NM_006186	5.15	5.52	0.933470433
NR4A2	NM_006186	4.88	5.68	0.859257687
NR5A1	NM_004959	1.55	1.88	0.827098402
NR5A1	NM_004959	1.56	1.94	0.806250074
NRL	M81840	1.12	1.36	0.824507422
NRL	M81840	1.08	1.34	0.802675923
NRsF form 2	U13879	1.51	1.60	0.940689035
NRsF form 2	U13879	1.29	1.56	0.826356612
NSEP1	NM_004559	4.08	4.54	0.898882683
NSEP1	NM_004559	4.09	4.85	0.843016697
nuclear factor 1 B-type	U07810	1.67	1.72	0.970651102
nuclear factor 1 B-type	U07810	1.50	1.56	0.957498055
nuclear factor I-B2	U85193	5.86	6.80	0.86191166
nuclear factor I-B2	U85193	6.04	7.09	0.85215085
nuclear factor IV	X57500	1.44	1.28	1.118113871
nuclear factor IV	X57500	1.35	1.53	0.882482444
OAZ	AF221712	0.95	0.98	0.974744849
OAZ	AF221712	0.82	0.94	0.867200363
Oct-1B=POU homeodomain	S66902	1.11	1.23	0.901795827
Oct-1B=POU homeodomain	S66902	1.07	1.22	0.879755632
Oct-4A	Z11900	1.44	1.75	0.825538314
Oct-4A	Z11900	1.43	1.85	0.773109431

OGL12	AF023203	2.31	2.68	0.864811744
OGL12	AF023203	2.45	2.92	0.837215348
OSMRB	U60805	0.90	1.09	0.825581
OSMRB	U60805	0.78	0.97	0.805457565
OTF3C	Z11901	6.19	4.42	1.40097838
OTF3C	Z11901	5.89	4.42	1.332945525
OTX1	AB037501	1.87	1.84	1.018457389
OTX1	AB037501	1.75	1.86	0.938379
OVOL1	NM_004561	1.34	1.20	1.12018921
OVOL1	NM_004561	1.05	1.21	0.869990813
p130	s67171	2.11	1.71	1.231079229
p130	s67171	1.56	1.60	0.975948711
p243	AJ242977	1.27	1.43	0.884227005
p243	AJ242977	1.37	1.69	0.812266478
P38IP	NM_017569	0.99	1.09	0.90720651
P38IP	NM_017569	0.94	1.10	0.856087428
p53	K03199	1.39	1.68	0.831158406
p53	K03199	1.38	1.67	0.828166161
p621	AJ242978	1.19	1.20	0.990516633
p621	AJ242978	1.06	1.18	0.898178687
PACE4	NM_002570	1.29	1.48	0.867988727
PACE4	NM_002570	1.26	1.48	0.852795758
PAX1	NM_006192	1.20	1.32	0.903818349
PAX1	NM_006192	1.06	1.32	0.807894213
PAX2	U45255	1.46	1.62	0.901165711
PAX2	U45255	1.40	1.63	0.858751434
PAX3	NM_000438	1.21	1.36	0.886358667
PAX3	NM_000438	1.16	1.37	0.850478749
PAX5	U56835	0.93	1.06	0.871188843
PAX5	NM_016734	1.71	2.02	0.846266
PAX6	U63833	1.33	1.53	0.865756264
PAX6	U63833	1.27	1.52	0.833925287
PAX8	S55490	1.94	2.07	0.934433059
PAX8	S55490	1.82	2.05	0.885815601
PAX9	NM_006194	0.78	0.95	0.817959194
PAX9	X92850	1.17	1.49	0.784900153
PBX1	NM_002585	1.46	1.26	1.160624187
PBX1	NM_002585	1.56	1.36	1.14486291
PBX2	NM_002586	1.14	1.28	0.885932245
PBX2	NM_002586	1.14	1.34	0.848773413
PC4	NM_006713	0.70	0.80	0.879994421
PC4	NM_006713	0.70	0.81	0.86301099
PCAF	NM_003884	1.07	1.34	0.798415415
PCAF	NM_003884	1.03	1.29	0.796481403
PDEF	NM_012391	1.17	1.33	0.876561702
PDEF	NM_012391	1.38	1.70	0.811137032
PEA3	D12765	1.21	1.54	0.784602478
PEA3	D12765	1.21	1.56	0.775569587
PEPD	J04605	0.66	0.78	0.8570049
PEPD	J04605	0.71	0.86	0.827558815

PGF	NM_002632	1.08	1.18	0.917061973
PGF	NM_002632	1.01	1.20	0.83593402
pGLI3HH	M20674	1.21	1.31	0.921799298
pGLI3HH	M20674	1.13	1.32	0.856812924
PIAS3	NM_006099	3.47	4.09	0.849170482
PIAS3	NM_006099	3.59	4.26	0.842175439
PINCH	U09284	1.62	1.49	1.088214315
PINCH	U09284	1.44	1.44	1.001116263
Pit-1	D10216	2.56	2.74	0.934572932
Pit-1	D10216	2.26	2.72	0.831778211
PITX1	NM_002653	1.04	1.23	0.841903944
PITX1	NM_002653	0.95	1.22	0.780247958
PITX2	U69961	2.17	1.90	1.142972468
PITX2	U69961	1.90	1.73	1.099447256
PITX3	NM_005029	1.08	1.19	0.908904038
PITX3	NM_005029	1.05	1.16	0.900257494
PKNOX1	NM_004571	2.66	2.91	0.915727678
PKNOX1	NM_004571	2.43	2.80	0.867326045
PLCG1	NM_002660	0.88	1.09	0.801330479
PLCG1	NM_002660	0.87	1.12	0.777390419
PML	M79462	2.93	3.22	0.90918611
PML	M79462	2.83	3.18	0.891376967
POU6F1	NM_002702	1.18	1.38	0.853348217
POU6F1	NM_002702	1.11	1.39	0.803725887
PPAR delta	AF187850	1.68	2.05	0.817974153
PPAR delta	AF187850	1.63	2.05	0.797208472
PPARbeta	L07592	1.12	1.30	0.860735779
PPARbeta	L07592	1.09	1.30	0.841097109
PPARBP	NM_004774	2.49	2.42	1.028888699
PPARBP	NM_004774	2.59	2.62	0.989587372
PPARG	NM_005037	1.76	1.92	0.919451555
PPARG	NM_005037	1.54	1.87	0.82431469
PPARGC1	NM_013261	4.02	4.08	0.985608174
PPARGC1	NM_013261	3.61	3.97	0.910308604
PPIH	NM_006347	1.11	1.36	0.810066673
PPIH	NM_006347	1.10	1.37	0.797849135
pRb	X16439	1.29	1.40	0.923240454
pRb	X16439	1.21	1.44	0.839720657
PRDM4	NM_012406	1.09	1.14	0.952491603
PRDM4	NM_012406	1.02	1.09	0.935085892
protein Id4	U28368	1.18	1.11	1.06450375
protein Id4	U28368	1.29	1.23	1.054319434
protein p38	AJ242975	1.63	1.95	0.834950074
protein p38	AJ242975	1.44	1.85	0.781801717
PRX2	NM_016307	4.82	3.63	1.326456916
PRX2	NM_016307	4.32	4.25	1.017671923
PSCDBP	NM_004288	0.74	0.85	0.86992699
PSCDBP	NM_004288	0.69	0.84	0.81936229
PSMC1	NM_002802	1.36	1.52	0.894759062
PSMC1	NM_002802	1.18	1.33	0.891456342

PTHR1	NM_000316	1.31	1.42	0.924499528
PTHR1	NM_000316	1.20	1.40	0.8556512
PXMP3	NM_000318	1.62	2.02	0.804068402
PXMP3	NM_000318	1.40	1.80	0.78066981
PXN	NM_002859	2.72	2.90	0.93925013
PXN	NM_002859	2.51	2.90	0.863012935
rab 13	X75593	1.25	1.23	1.008775651
rab 13	X75593	1.12	1.33	0.83974611
RAR-alpha1	X06614	1.43	1.62	0.88166305
RAR-alpha1	X06614	1.30	1.60	0.814209521
RAR-b	M96016	1.57	1.95	0.801619789
RAR-b	M96016	1.57	2.00	0.782949951
RARA	NM_000964	1.42	1.65	0.862685131
RARA	NM_000964	1.40	1.65	0.847918555
RARG	NM_000966	1.42	1.61	0.882296859
RARG	NM_000966	1.41	1.60	0.882261145
RB1	NM_000321	0.97	1.19	0.812728745
RB1	NM_000321	0.96	1.20	0.800478062
RBL1	NM_002895	2.04	2.42	0.841470759
RBL1	NM_002895	1.92	2.35	0.817621225
RBP-L	AB026048	0.94	0.70	1.339824561
RBP-L	AB026048	0.80	0.71	1.133824475
RCL	NM_006443	1.26	1.39	0.906711617
RCL	NM_006443	1.24	1.39	0.891529469
RELA	Z22951	0.86	0.89	0.96567493
RELA	Z22951	0.80	0.85	0.94852389
repressor protein	D30612	1.37	1.53	0.890929984
repressor protein	D30612	1.32	1.52	0.87316143
REQ	NM_006268	1.43	1.67	0.860238236
REQ	NM_006268	1.46	1.72	0.847602428
retinoid X receptor alpha	U66306	2.17	2.44	0.889382828
retinoid X receptor-gamma	U38480	2.07	2.33	0.889199662
RFP	NM_006510	3.73	3.97	0.940382915
RFP	NM_006510	3.81	4.43	0.858648769
RFX3	X76092	1.62	1.47	1.1024024
RFX3	X76092	1.43	1.62	0.8816817
rhoHP1	D85815	1.42	1.33	1.069393174
rhoHP1	D85815	1.46	1.53	0.955107329
RING1	NM_002931	1.42	1.59	0.896164283
RING1	NM_002931	1.41	1.60	0.880810591
RLF	NM_012421	3.38	3.75	0.901013305
RLF	NM_012421	3.65	4.07	0.898102049
RNF NY-REN-43	AF155109	1.18	1.29	0.913146151
RNF NY-REN-43	AF155109	1.16	1.43	0.811644103
RNF13	NM_007282	1.22	1.33	0.916119358
RNF13	NM_007282	1.20	1.31	0.912867135
RNF15	NM_006355	1.29	1.45	0.893216374
RNF15	NM_006355	1.17	1.44	0.811128245
RNF4	NM_002938	1.35	1.44	0.936370857

RNF4	NM_002938	1.32	1.45	0.907740218
RNF9	NM_006778	1.25	1.36	0.918123369
RNF9	NM_006778	1.18	1.36	0.863185084
RNP-specific A	X06347	1.31	1.39	0.94551044
RNP-specific A	X06347	1.16	1.47	0.788038353
RORalpha2	U04898	4.15	4.42	0.938764319
RORalpha2	U04898	4.03	4.29	0.938708029
RORbeta	Y08639	1.29	1.50	0.858111801
RORbeta	Y08639	1.27	1.50	0.842642276
RORC	NM_005060	1.39	1.61	0.861315789
RORC	NM_005060	1.43	1.77	0.807520338
RP58	AJ223321	1.34	1.40	0.953320654
RP58	AJ223321	1.19	1.38	0.866072097
RPF-1	U91934	1.26	1.51	0.833565324
RPF-1	U91934	1.23	1.50	0.822227125
RPL13A	X56932	0.87	0.88	0.991870123
RPL13A	X56932	0.77	0.87	0.883814097
RPL15	NM_002948	1.01	1.07	0.944600915
RPL15	NM_002948	0.98	1.14	0.859452181
RPL21	NM_000982	1.60	1.53	1.04809166
RPL21	NM_000982	1.57	1.58	0.995425213
RPL23A	NM_000984	1.59	1.42	1.117137899
RPL23A	NM_000984	1.46	1.38	1.059317332
RPL37	NM_000997	1.09	1.23	0.883744302
RPL37	NM_000997	1.09	1.30	0.842639916
RPS11	NM_001015	1.55	1.32	1.171184602
RPS11	NM_001015	1.30	1.22	1.068789518
RPS19	NM_001022	0.84	1.00	0.841774594
RPS19	NM_001022	0.86	1.05	0.819892642
RRN3	NM_018427	1.64	1.61	1.015843155
RRN3	NM_018427	1.10	1.40	0.78552954
RUVBL1	NM_003707	1.21	1.41	0.864080705
RUVBL1	NM_003707	1.15	1.43	0.805614035
Rx	AF001911	1.40	1.19	1.169408279
Rx	AF001911	1.21	1.29	0.940515001
RXR-alpha	X52773	1.14	1.20	0.95178794
RXR-alpha	X52773	1.02	1.17	0.875212013
RXRB	U00961	1.41	1.76	0.802764083
RXRB	U00961	1.32	1.64	0.802187954
SAFB	NM_002967	2.08	1.85	1.122521568
SAFB	NM_002967	1.98	1.85	1.072239203
SALL1	NM_002968	1.06	1.32	0.799379966
SALL1	NM_002968	1.09	1.37	0.794919835
sAP-1a	M85165	1.02	1.15	0.893216374
sAP-1a	M85165	0.99	1.14	0.868660598
SEP3B	AF285109	1.36	1.52	0.895524427
SEP3B	AF285109	1.34	1.51	0.891662954
sF1	D88155	1.24	1.23	1.006655807
sF1	D88155	0.89	1.10	0.815406356
SF3A1	NM_005877	0.94	1.18	0.796947498

SF3A1	NM_005877	0.98	1.24	0.789354005
SIX1	X91868	1.28	1.26	1.011940877
SIX1	X91868	1.15	1.27	0.899649002
SIX6	AF141651	1.31	1.51	0.866808238
SIX6	AF141651	1.28	1.61	0.795100562
SKI	NM_003036	1.27	1.34	0.951830965
SKI	NM_003036	1.23	1.34	0.916814067
SKIL	NM_005414	1.22	1.23	0.996060051
SKIL	NM_005414	1.18	1.23	0.965665088
Smad2	U78726	1.54	1.70	0.902843033
Smad2	U78726	1.52	1.74	0.876401307
SMARCA3	NM_003071	2.60	2.63	0.988267744
SMARCA3	NM_003071	2.52	2.58	0.977550509
SMARCA4	NM_003072	1.20	1.41	0.850958457
SMARCA4	NM_003072	1.14	1.43	0.798506046
SMARCC1	NM_003074	1.37	1.53	0.897049921
SMARCC1	NM_003074	1.31	1.51	0.867695906
SMARCC2	NM_003075	1.11	1.36	0.816630385
SMARCC2	NM_003075	1.10	1.37	0.803295263
SMN1	U18423	2.14	2.06	1.0410434
SMN1	U18423	1.93	2.06	0.938075938
SNAP190	AF032387	1.08	1.15	0.940066948
SNAP190	AF032387	1.19	1.34	0.88972042
SNAPC3	NM_003084	0.64	0.65	0.973605848
SNAPC3	NM_003084	0.58	0.67	0.873988625
snRNP B	X17567	0.99	0.98	1.010085806
snRNP B	X17567	0.82	0.97	0.840177885
SOX10	AJ001183	1.71	1.82	0.937524016
SOX10	AJ001183	1.59	1.78	0.894532832
SOX13	NM_005686	1.71	1.92	0.891384762
SOX13	NM_005686	1.66	1.93	0.860515571
SOX4	X70683	0.90	0.93	0.960960313
SOX4	X70683	0.82	0.92	0.894488762
SOX6	X65663	0.69	0.79	0.882795517
SOX6	X65663	0.65	0.75	0.87280897
SOX8	AF164104	1.79	2.09	0.857375717
SOX8	AF164104	1.65	2.13	0.774778844
SOX9	Z46629	1.69	1.88	0.898185589
SOX9	Z46629	1.55	1.92	0.807916038
SP1	J03133	1.18	1.30	0.909375062
SP1	J03133	1.16	1.30	0.887824726
SP3	X68560	1.66	1.66	1.001079125
SP3	X68560	1.45	1.77	0.818395433
sRF	J03161	1.45	1.67	0.867315899
sRF	J03161	1.43	1.69	0.84824421
sRY	L10101	1.18	1.21	0.982441028
sRY	L10101	1.13	1.21	0.934783803
STAT2	M97934	1.41	1.52	0.926980567
STAT2	M97934	1.41	1.62	0.868724958
STAT5B	NM_012448	1.56	1.40	1.114847778

STAT5B	NM_012448	1.40	1.71	0.821978259
STAT6	NM_003153	1.27	1.36	0.938049629
STAT6	NM_003153	1.21	1.37	0.879605458
SZF1	NM_016089	1.21	1.50	0.802961061
SZF1	NM_016089	1.16	1.49	0.774800507
T-STAR	NM_006558	0.67	0.78	0.861849244
T-STAR	NM_006558	0.68	0.82	0.831664605
T3R	Y00479	1.71	1.62	1.053389262
T3R	Y00479	1.60	1.53	1.041322337
T3R	X55066	1.56	1.89	0.824459774
TAF(I)63	L39061	1.00	1.12	0.896350467
TAF(I)63	L39061	1.02	1.30	0.783696377
TAF(II)30	U25816	1.51	1.40	1.074026032
TAF(II)30	U25816	1.40	1.38	1.015134059
TAF(II)32	U21858	0.98	1.22	0.802461769
TAF(II)32	U21858	0.98	1.23	0.792812413
TAF(II)70-alpha	L25444	0.96	1.02	0.941312641
TAF(II)70-alpha	L25444	0.90	1.03	0.872787029
TAF2A	NM_004606	1.13	1.14	0.999330892
TAF2A	NM_004606	0.93	1.11	0.838249213
TAF2F	NM_005642	1.03	1.26	0.81530342
TAF2F	NM_005642	1.02	1.30	0.784947723
TAF2I	NM_005643	1.50	1.43	1.045218429
TAF2I	NM_005643	1.39	1.41	0.991353741
TAF2I	AF118094	1.11	1.26	0.881120736
TAF2J	NM_005644	1.28	1.40	0.913232427
TAF2J	NM_005644	1.23	1.45	0.849684168
TAF2K	NM_005645	2.39	2.40	0.997067405
TAF2K	NM_005645	2.40	2.47	0.972697492
TAFII105	Y09321	1.26	1.45	0.867396208
TAFII105	Y09321	1.19	1.45	0.818176516
Tal-1	NM_003189	1.37	1.51	0.902488517
Tal-1	NM_003189	1.27	1.53	0.828923165
TARBP2	NM_004178	1.09	1.24	0.873471591
TARBP2	NM_004178	1.08	1.37	0.786576406
TBP	NM_003194	2.77	2.67	1.040623399
TBP	NM_003194	2.51	2.58	0.973841382
TBPL1	NM_004865	1.28	1.30	0.987855849
TBPL1	NM_004865	1.11	1.40	0.794804113
TBR1	NM_006593	1.19	1.20	0.996692807
TBR1	NM_006593	1.05	1.26	0.836636729
TBX19	NM_005149	1.36	1.48	0.923280344
TBX19	NM_005149	1.44	1.59	0.909429873
TBX2	NM_005994	0.85	1.07	0.798962867
TBX2	NM_005994	0.83	1.06	0.785853316
TBX20	AJ237589	1.34	1.21	1.102533818
TBX20	AJ237589	1.36	1.64	0.831910222
TBX6	NM_004608	4.15	4.62	0.899551242
TBX6	NM_004608	3.96	4.53	0.875140298
TCEA1	NM_006756	1.27	1.14	1.110125734

TCEA1	NM_006756	1.16	1.11	1.05196336
TCEB2	NM_007108	0.58	0.43	1.337134151
TCEB2	NM_007108	0.51	0.40	1.277713489
TCF-1	Z47365	1.00	1.16	0.86404602
TCF-1	Z47365	0.92	1.18	0.774647829
TCF-4	Y11306	1.36	1.46	0.928464375
TCF-4	Y11306	1.32	1.56	0.849608167
TCF21	NM_003206	1.75	2.02	0.863693344
TCF21	NM_003206	1.69	2.12	0.798699048
TCF4	NM_003199	0.93	0.92	1.021001263
TCF4	NM_003199	0.84	0.92	0.912194059
TCF6L1	NM_003201	1.67	1.95	0.857799865
TCF6L1	NM_003201	1.82	2.34	0.776883554
TCFL1	NM_005997	1.45	1.63	0.891060583
TCFL1	NM_005997	1.45	1.68	0.863907712
TCFL5	NM_006602	1.87	2.31	0.809256058
TCFL5	NM_006602	1.79	2.27	0.788010751
TEAD1	M63896	1.97	2.40	0.821174945
TEAD1	M63896	1.84	2.35	0.783305005
TEF-4	X94440	1.14	1.29	0.883210896
TEF-4	X94440	1.13	1.33	0.854457478
TF	U79243	1.42	1.54	0.919800195
TF	U79243	1.29	1.63	0.789904601
TFCP2	NM_005653	0.99	1.11	0.887949768
TFCP2	NM_005653	0.94	1.13	0.832221275
TFE3	AL161985	1.20	1.25	0.952888449
TFE3	AL161985	1.16	1.30	0.896818053
TFIIA	NM_015859	0.84	0.82	1.018380452
TFIIA	NM_015859	0.80	0.82	0.977671128
TFIID	Z22828	2.50	2.34	1.068758898
TFIID	Z22828	2.55	2.73	0.936976254
TFIIH-cyclin H	U11791	1.28	0.95	1.34843684
TFIIH-cyclin H	U11791	1.29	0.98	1.318842969
TFIIH-MO15	X77743	2.43	2.39	1.014330459
TFIIH-MO15	X77743	2.43	2.39	1.012865369
TFIIH-p34	Z30093	2.74	2.96	0.92722107
TFIIH-p34	Z30093	2.34	2.95	0.792209645
TFRC	NM_003234	1.33	1.49	0.895571075
TFRC	NM_003234	1.28	1.59	0.809200973
TGIF	NM_003244	1.75	1.38	1.274809288
TGIF	NM_003244	1.52	1.51	1.004868421
TIEG2	NM_003597	1.39	1.48	0.938352308
TIEG2	NM_003597	1.35	1.51	0.889349637
TIF1GAMMA	NM_015906	1.01	1.27	0.800846532
TIF1GAMMA	NM_015906	1.01	1.30	0.777179202
TIF2	X97674	1.33	1.45	0.922316636
TIF2	X97674	1.31	1.45	0.902108121
TIM44	NM_006351	1.33	1.57	0.847735407
TIM44	NM_006351	1.36	1.61	0.84323103
Timeless	AF098162	2.00	2.39	0.833636058

Timeless	AF098162	1.93	2.42	0.796169622
TIMM8b	AF152350	1.40	1.42	0.984849477
TIMM8b	AF152350	1.42	1.51	0.941288783
TIMM9	NM_012460	0.71	0.77	0.920513309
TIMM9	NM_012460	0.68	0.84	0.805700618
Tis11d	U07802	1.12	1.35	0.827564107
Tis11d	U07802	1.04	1.27	0.821167897
TNRC11	NM_005120	0.88	1.05	0.836486567
TNRC11	NM_005120	0.85	1.05	0.802230359
TOB1	NM_005749	1.02	1.29	0.790953507
TOB1	NM_005749	1.02	1.32	0.77856472
TOP1	U07806	3.49	3.40	1.026563028
TOP1	U07806	3.18	3.15	1.008577791
TP53BP1	NM_005657	0.83	0.86	0.969466553
TP53BP1	NM_005657	0.79	0.86	0.910836728
TP73	NM_005427	4.36	4.73	0.923146915
TP73	NM_005427	3.95	4.55	0.867754692
TR2	AF171055	1.60	1.59	1.007806633
TR2	AF171055	1.53	1.69	0.90288023
TRAF6	NM_004620	1.25	1.38	0.902520712
TRAF6	NM_004620	1.33	1.62	0.825230675
TTF-1	U43203	1.57	1.92	0.818730798
TTF-1	U43203	1.59	1.97	0.8042506
TTF-I interacting peptide	AF000560	0.93	1.01	0.912809508
TTF-I interacting peptide	AF000560	0.92	1.02	0.908180051
TTF1	NM_007344	1.36	1.32	1.03206288
TTF1	NM_007344	1.21	1.33	0.908191402
TTP	M63625	1.47	1.69	0.871059069
TTP	M63625	1.45	1.78	0.812551459
tumor suppressor	AJ224819	0.97	0.96	1.010680445
tumor suppressor	AJ224819	0.94	0.94	1.002997158
twist	X91662	1.15	1.30	0.889607419
twist	X91662	1.14	1.32	0.862171118
TZFP	NM_014383	1.61	1.57	1.026900096
TZFP	NM_014383	1.31	1.62	0.806125978
ubiquitin	M26880	1.25	1.29	0.968558812
ubiquitin	M26880	1.20	1.38	0.866123555
UBP1	NM_014517	1.16	1.39	0.837548498
UBP1	NM_014517	1.05	1.31	0.801834157
UKLF	AB015132	0.94	1.15	0.812199016
UKLF	AB015132	0.91	1.13	0.807110731
UsF1	X55666	0.92	0.77	1.202641159
UsF1	X55666	0.90	1.16	0.779296001
UsF2	X90824	1.70	1.51	1.12444728
UsF2	X90824	1.49	1.47	1.010033818
UTF1	NM_003577	0.78	0.92	0.852557876
UTF1	NM_003577	0.75	0.88	0.846901451
Vax-2	Y17791	1.95	1.73	1.125466134
Vax-2	Y17791	1.50	1.58	0.944890049

VDR	NM_000376	2.14	1.94	1.102535767
VDR	NM_000376	2.17	1.98	1.096166462
Vimentin	X56134	0.85	0.82	1.03779146
Vimentin	X56134	0.77	0.78	0.995470101
VSX1	NM_014588	1.19	1.38	0.862794625
VSX1	NM_014588	1.14	1.36	0.838036984
WAVE2	AB026542	1.37	1.57	0.873152446
WAVE2	AB026542	1.34	1.56	0.8602453
Whn	Y11746	0.95	1.05	0.89877812
Whn	Y11739	0.98	1.10	0.8889781
winged-helix TFforkhead 5	AF055080	1.80	1.62	1.112375194
winged-helix TFforkhead 5	AF055080	1.64	1.65	0.995925632
XB	U52701	0.93	1.00	0.931696975
XB	U52701	0.86	0.99	0.874287286
XBP1	NM_005080	1.32	1.48	0.894006132
XBP1	NM_005080	1.29	1.50	0.861985033
XG	Z48514	0.94	1.07	0.879021004
XG	Z48514	0.94	1.11	0.844934408
XPE-BF	U32986	1.23	1.06	1.157546744
XPE-BF	U32986	1.11	1.18	0.939655721
XPOT	NM_007235	0.93	1.04	0.888739099
XPOT	NM_007235	0.91	1.09	0.833312043
YAF2	U72209	1.78	1.60	1.115424048
YAF2	U72209	1.29	1.55	0.831250433
YPT3	X79780	1.04	1.04	0.999551657
YPT3	X79780	0.91	1.09	0.841560488
YWHAZ	NM_003406	1.42	1.48	0.955552146
YWHAZ	NM_003406	1.34	1.45	0.924713154
ZFD25	AB027251	1.38	1.47	0.935259419
ZFD25	AB027251	1.38	1.59	0.867549237
ZFM1	D26120	1.38	1.52	0.904756638
ZFM1	D26120	1.32	1.51	0.870056053
ZFN3	X60153	1.11	1.27	0.873020321
ZFN3	X60153	1.08	1.27	0.84639825
ZFN5128	NM_014347	1.68	1.48	1.132667677
ZFN5128	NM_014347	1.69	1.51	1.116327465
ZFP161	NM_003409	1.54	1.51	1.021814742
ZFP161	NM_003409	1.53	1.56	0.977142745
ZFP36	NM_003407	1.35	1.21	1.119420521
ZFP36	NM_003407	1.40	1.26	1.107958549
ZFP37	NM_003408	2.85	3.53	0.806477053
ZFP37	NM_003408	3.00	3.78	0.795656333
ZFS-2	D70832	1.25	1.31	0.960341853
ZFS-2	D70832	1.19	1.34	0.887098454
zinc finger factor GKLF	AF105036	2.60	2.44	1.066684361
zinc finger factor GKLF	AF105036	2.21	2.60	0.850960542
ZK1	NM_005815	1.09	1.29	0.849600519
ZK1	NM_005815	1.13	1.34	0.848599298
ZMPSTE24	NM_005857	1.59	1.96	0.807467602

ZMPSTE24	NM_005857	1.64	2.04	0.804181945
ZNF	AF024700	1.37	1.42	0.968200406
ZNF	AF024700	1.25	1.43	0.877660819
ZNF	AF024702	2.44	2.27	1.071242218
ZNF	AF024702	2.13	2.46	0.864203489
ZNF	AF024708	0.85	1.06	0.803894737
ZNF	AF024708	0.88	1.10	0.795504238
ZNF	AF244088	0.96	1.18	0.80824225
ZNF	AL359576	1.96	2.40	0.816139265
ZNF	AL359576	1.97	2.45	0.804419877
ZNF	L14787	0.81	0.94	0.858334842
ZNF	L14787	0.77	0.99	0.776247563
ZNF	L14843	1.04	1.21	0.859382421
ZNF	L14843	1.00	1.22	0.819499696
ZNF	M77171	0.87	1.07	0.819786317
ZNF	M77171	0.84	1.06	0.788842997
ZNF	M77172	1.11	1.29	0.86138076
ZNF	M77172	1.10	1.31	0.841409825
ZNF	U69645	1.02	1.11	0.923798753
ZNF	U69645	1.01	1.10	0.92309697
ZNF	U90919	1.91	2.41	0.791009945
ZNF	X16282	1.04	1.06	0.976817907
ZNF	X16282	0.97	1.08	0.896468376
ZNF H140	U80232	1.31	1.38	0.951857602
ZNF H140	U80232	1.25	1.46	0.852470368
ZNF RIZ	U17838	1.37	1.49	0.919856161
ZNF RIZ	U17838	1.33	1.52	0.878560838
ZNF10	NM_003419	1.14	1.24	0.918736842
ZNF10	NM_003419	1.06	1.25	0.852019812
ZNF124	NM_003431	1.66	1.70	0.976675202
ZNF124	NM_003431	1.69	1.79	0.942839506
ZNF131	U09410	4.06	3.16	1.287565844
ZNF131	U09410	3.52	3.10	1.135482919
ZNF132	NM_003433	1.58	1.92	0.819592954
ZNF132	NM_003433	1.39	1.80	0.770618048
ZNF133	NM_003434	1.00	1.08	0.92665805
ZNF133	NM_003434	0.98	1.07	0.917239309
ZNF133	U09366	1.59	1.48	1.074070972
ZNF133	U09366	1.44	1.60	0.901250209
ZNF134	NM_003435	0.87	1.03	0.842143011
ZNF134	NM_003435	0.89	1.11	0.803684073
ZNF135	NM_003436	1.21	1.31	0.927158596
ZNF136	NM_003437	1.76	1.84	0.953483104
ZNF136	NM_003437	1.71	1.96	0.871707485
ZNF139	U09848	1.82	2.14	0.854333258
ZNF139	U09848	1.88	2.25	0.83696718
ZNF140	NM_003440	1.18	1.31	0.902148538
ZNF140	NM_003440	1.10	1.38	0.795943758
ZNF141	NM_003441	0.94	1.10	0.852952765
ZNF141	NM_003441	0.97	1.14	0.851266923

ZNF143	NM_003442	1.23	1.38	0.888983121
ZNF143	NM_003442	1.25	1.41	0.88328255
ZNF144	NM_007144	1.39	1.50	0.928320948
ZNF144	NM_007144	1.37	1.47	0.926533504
ZNF146	NM_007145	2.27	2.48	0.916337136
ZNF146	NM_007145	2.13	2.64	0.805090416
ZNF154	U20648	1.01	1.10	0.91658232
ZNF154	U20648	0.98	1.10	0.890033893
ZNF157	NM_003446	3.06	3.63	0.842644802
ZNF157	NM_003446	3.32	4.07	0.815095843
ZNF169	U28251	1.07	1.06	1.007079353
ZNF169	U28251	0.99	1.12	0.884849008
ZNF173	NM_003449	1.76	1.84	0.954247529
ZNF173	NM_003449	1.69	1.91	0.885869838
ZNF174	U31248	1.05	1.11	0.946809357
ZNF174	U31248	0.98	1.07	0.916147357
ZNF175	NM_007147	1.42	1.58	0.896913462
ZNF175	NM_007147	1.37	1.66	0.824940576
ZNF177	NM_003451	1.35	1.31	1.030771696
ZNF177	NM_003451	1.16	1.36	0.850314531
ZNF180	NM_013256	0.97	1.13	0.856084978
ZNF180	NM_013256	0.97	1.18	0.824583936
ZNF186	NM_012480	1.05	1.14	0.913656108
ZNF186	NM_012480	0.99	1.11	0.892164294
ZNF191	AF016052	3.91	4.38	0.892949504
ZNF191	AF016052	4.30	5.22	0.823076704
ZNF200	NM_003454	1.53	1.36	1.124250225
ZNF200	NM_003454	1.47	1.43	1.02397083
ZNF211	NM_006385	2.54	2.24	1.133216101
ZNF211	NM_006385	2.36	2.13	1.105677798
ZNF214	NM_013249	1.12	1.35	0.833321399
ZNF214	NM_013249	1.15	1.43	0.806432749
ZNF215	NM_013250	1.09	1.24	0.879083204
ZNF215	NM_013250	1.13	1.35	0.837769383
ZNF216	AF062073	6.28	6.85	0.916789497
ZNF216	AF062073	6.12	6.94	0.882430365
ZNF22	NM_006963	1.06	1.27	0.835382221
ZNF22	NM_006963	1.05	1.29	0.80987367
ZNF220	NM_006766	1.16	1.31	0.88697634
ZNF220	NM_006766	1.15	1.35	0.848209348
ZNF223	NM_013361	1.29	1.44	0.90055118
ZNF223	NM_013361	1.25	1.45	0.865757643
ZNF228	NM_013380	1.13	1.10	1.028423144
ZNF228	NM_013380	0.84	1.00	0.838339028
ZNF229	AF192979	1.44	1.74	0.826578529
ZNF229	AF192979	1.41	1.76	0.802898585
ZNF231	NM_003458	1.29	1.38	0.933778707
ZNF231	NM_003458	1.24	1.42	0.875912367
ZNF232	NM_014519	3.91	3.54	1.103967871
ZNF232	NM_014519	3.65	3.40	1.074957509

ZNF232	AF080171	0.94	1.07	0.871430609
ZNF232	AF080171	0.92	1.08	0.856315576
ZNF258	NM_007167	3.65	2.56	1.429969861
ZNF258	NM_007167	2.86	2.23	1.280364117
ZNF261	NM_005096	2.03	2.19	0.929608653
ZNF261	NM_005096	1.79	2.05	0.873798627
ZNF297	NM_005453	1.40	1.66	0.844649054
ZNF297	NM_005453	1.39	1.65	0.841507575
ZNF31	U71600	0.91	1.13	0.804205241
ZNF31	U71600	0.89	1.16	0.770222697
ZNF35	NM_003420	1.53	1.57	0.977397734
ZNF35	NM_003420	1.52	1.62	0.938058006
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ZYX	NM_003461	1.40	1.36	1.031031823
ZYX	NM_003461	1.31	1.36	0.963983275

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WHAT IS CLAIMED IS:

1. A method for providing an internal standard for normalizing the relative intensities of signals on a hybridization array, comprising:

adding a known quantity of an unlabelled ribosomal nucleic acid competitor probe into a hybridization buffer suitable for the array experiment, the competitor probe characterized in that it has the same as a portion of a capture probe present in the array for immobilizing ribosomal nucleic acids thereon; and

allowing the competitor probe to compete with a ribosomal capture probe for hybridization to a suitably labelled rRNA-derived cDNA of a cDNA sample, such that a hybridization signal of labelled rRNA-derived cDNA is decreased to a suitable signal dynamic range of detection and the rRNA-derived cDNA of the sample becomes a suitable internal standard for the hybridization array.

2. A method for normalizing the relative intensities of signals on a hybridization array, comprising:

reproducing the method of claim 1 with a first reference sample labelled with a first label, and with a second test sample labelled with a second label; and

comparing the intensity of a hybridization signal of hybridized rRNA-derived cDNA originating from the test sample to the intensity of a hybridization signal of hybridized rRNA-derived cDNA originating from the reference sample, to obtain a normalization factor.

3. A hybridization assay comprising:

reproducing the method of claim 2; and

normalizing the signals provided for each label for a given target nucleic acid hybridizing to a target-specific capture probe, said target originating from the reference and being

labelled with the first label and from the test sample and being labelled with the second label, with the normalization factor.

4. A method as defined in any one of claims 1 to 3, further comprising:

determining the quantity of hybridized rRNA-derived cDNA.

5. A method as defined in claim 4, further comprising:

comparing the quantity of hybridized rRNA-derived cDNA against standard curves to determine the quantity of cDNA in said sample.

6. A method as described in any one of claims 1 to 5, wherein said rRNA competitor probe is present in a concentration that is about 5 to about 100 times that of the rRNA-cDNA probe.

7. A method as described in anyone of claims 1 to 6, wherein said rRNA-derived cDNA is labelled by 3' addition of phosphate, cyanines, biotin, digoxygenin, fluorescein, a dideoxynucleotide, an amine, a thiol, an azo (N_3) group, fluorine, or any other form of label.

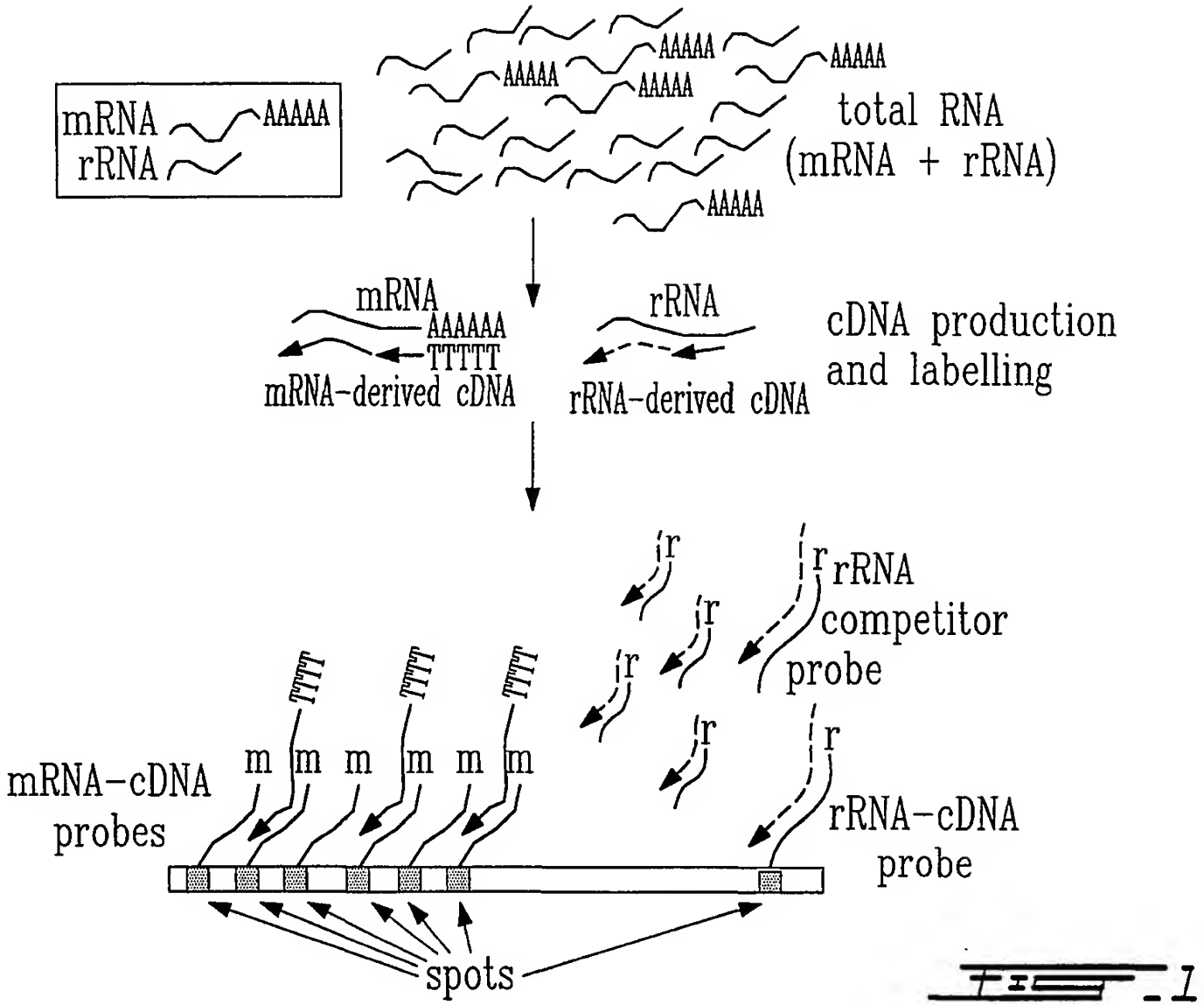
8. A method as described in any one of claims 1 to 7, which is used in high-throughput screening.

9. A method as described in any one of claims 1 to 8, wherein said array experiment consists in the identification of sequences found in the open reading frame of genes coding for transcription factors.

10. A method as described in claim 8, wherein said transcription factors include c-Rel, E2F-1, Egr-1, ER, NFκB p50, p53, Sp1 and YY1.

11. A solid support displaying an array of probes bound thereto, which array comprises a capture probe complementary to ribosomal nucleic acids or to cDNA derived therefrom.

12. A hybridization kit which comprises the solid support of claim 11 and, as a separate component, a competitor probe, the sequence of which comprises a least a portion of the sequence of the capture probe.


mRNA
rRNA
AAAAA
AAAAA
AAAAA
AAAAA
AAAAA
AAAAA
total RNA
(mRNA + rRNA)
mRNA
AAAAAA
TTTTT
mRNA-derived cDNA
rRNA
rRNA-derived cDNA
cDNA production
and labelling
r
r
r
r
r
r
rRNA
competitor
probe
TTT
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probes
r
rRNA-cDNA
probe
spots

Fig. 1

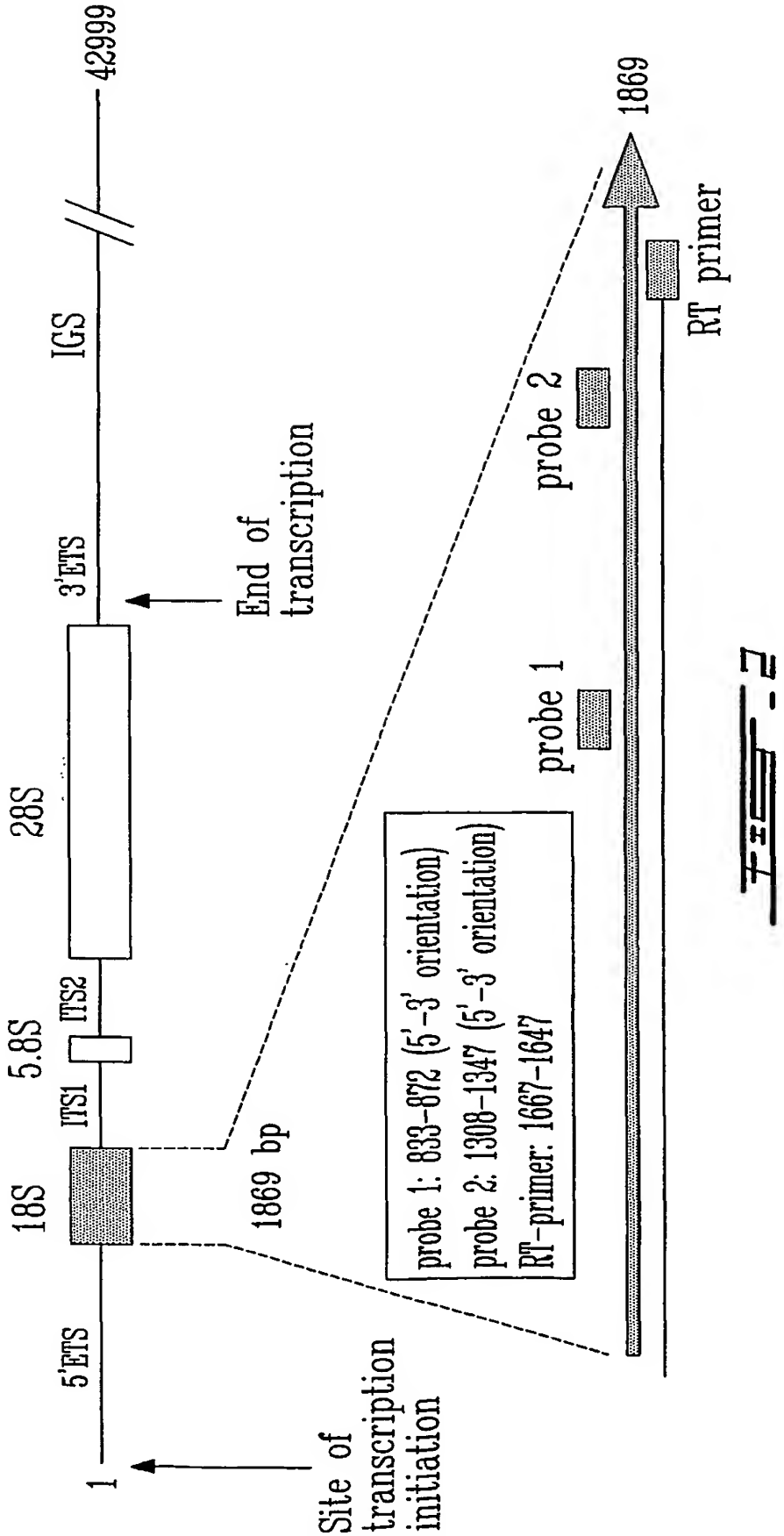
1
Site of transcription initiation
5'ETS
18S
ITS1
5.8S
ITS2
28S
3'ETS
End of transcription
IGS
42999
1869 bp
probe 1: 833-872 (5'-3' orientation)
probe 2: 1308-1347 (5'-3' orientation)
RT-primer: 1667-1647
probe 1
probe 2
1869
RT primer

Fig. 2

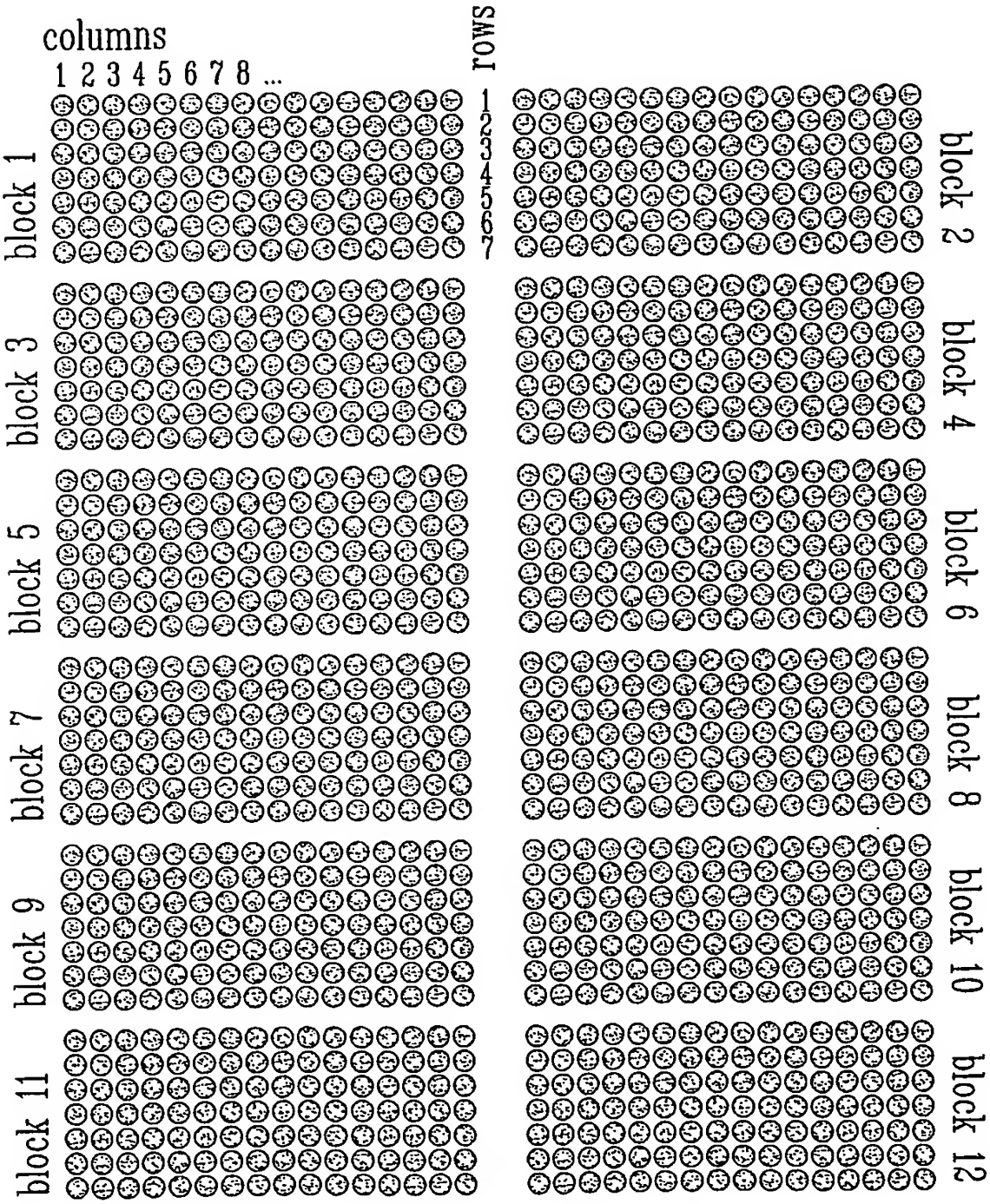
columns
1 2 3 4 5 6 7 8 ...
rows
1
2
3
4
5
6
7
block 1
block 2
block 3
block 4
block 5
block 6
block 7
block 8
block 9
block 10
block 11
block 12

Fig. 3

FIG 4

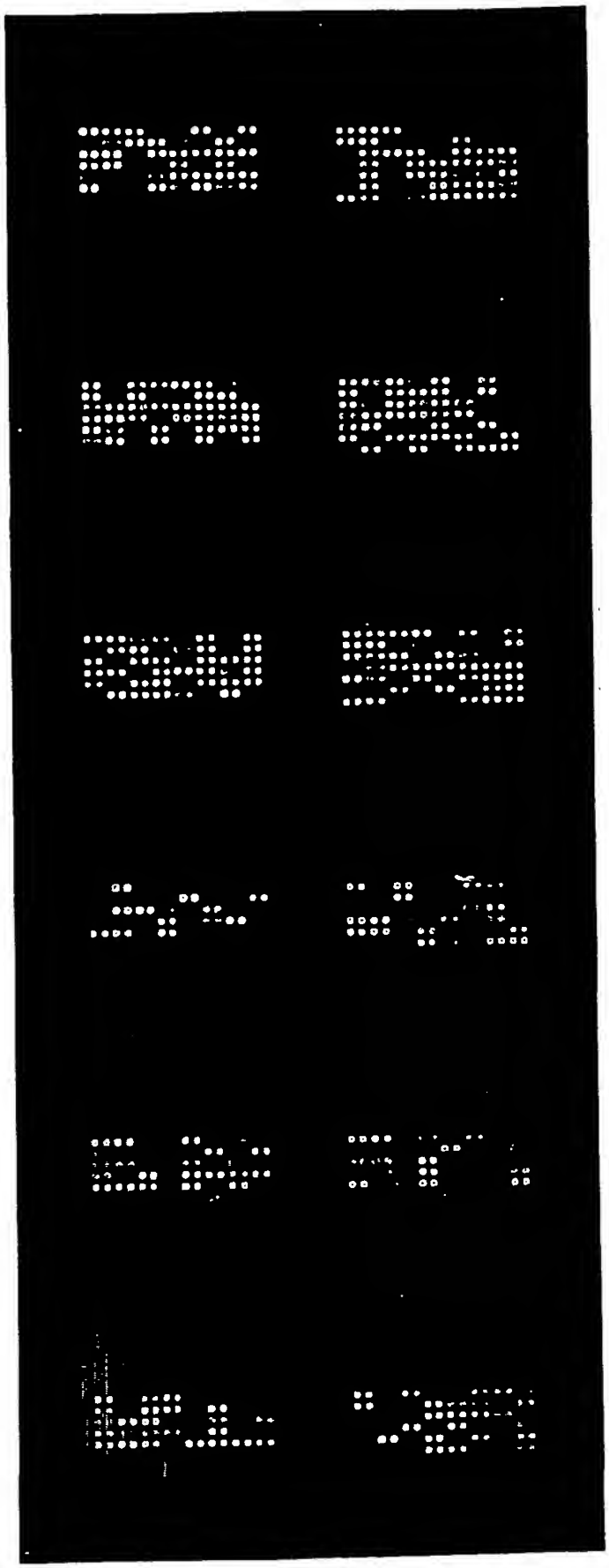

FIG. 5

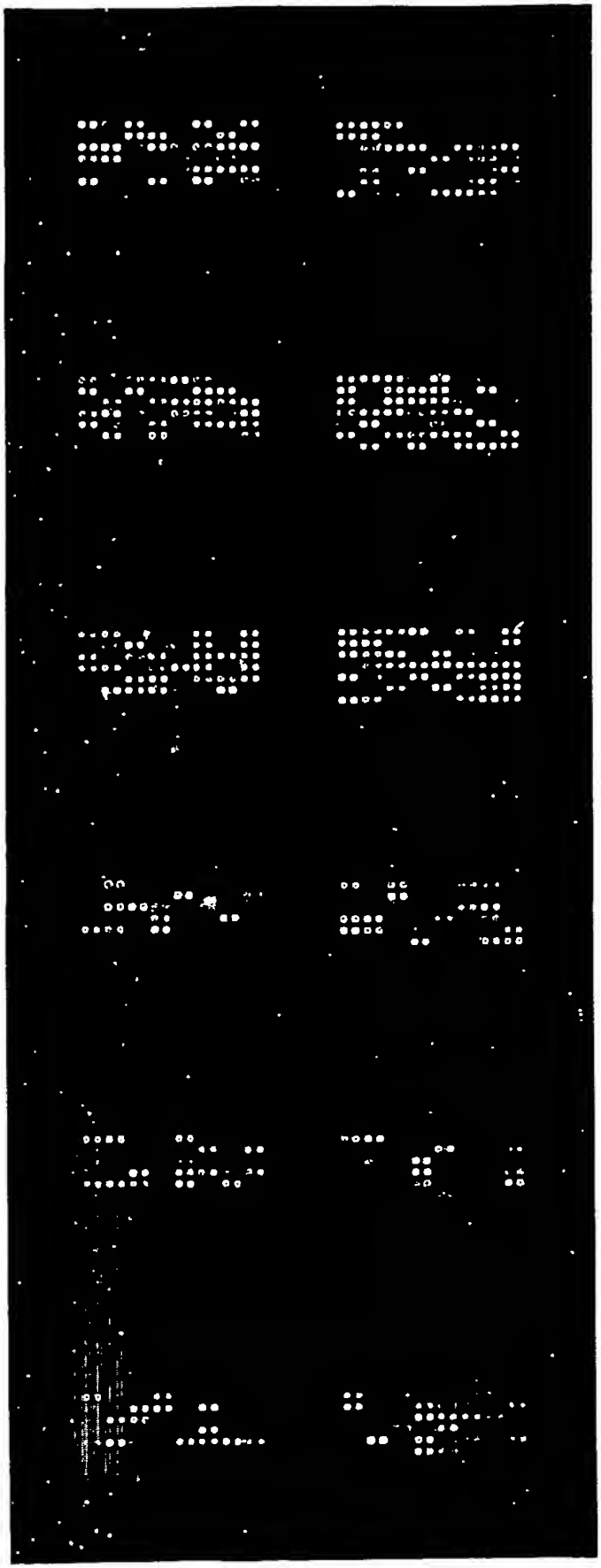

FIG. 6

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* KB/11912.32

Box No. I TITLE OF INVENTION

METHOD FOR NORMALIZING THE RELATIVE INTENSITIES OF DETECTION SIGNALS IN HYBRIDIZATION ARRAYS

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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5445, avenue de Lorimier, bureau 401
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H2H 2S5
CANADA

Telephone No. (514) 528-9233

Facsimile No. (514) 528-9225

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: CA

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LAROSE, Anne-Marie
5320 13ème Avenue
Montreal, Quebec
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CANADA

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: CA

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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Telephone No. (514) 397-7604

Facsimile No. (514) 397-4382

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LEBLANC, Benoît
14893 Sherbrooke est
Montreal, Quebec
H1A 5K1
CANADA

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: CA

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CAMATO, Rino
8780 Narbonne
St-Leonard, Quebec
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This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: CA

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ■ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ■ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ■ **EP** **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ■ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ■ **AE** United Arab Emirates
- ■ **AG** Antigua and Barbuda
- ■ **AL** Albania
- ■ **AM** Armenia
- ■ **AT** Austria
- ■ **AU** Australia
- ■ **AZ** Azerbaijan
- ■ **BA** Bosnia and Herzegovina
- ■ **BB** Barbados
- ■ **BG** Bulgaria
- ■ **BR** Brazil
- ■ **BY** Belarus
- ■ **BZ** Belize
- ■ **CA** Canada
- ■ **CH & LI** Switzerland and Liechtenstein
- ■ **CN** China
- ■ **CO** Colombia
- ■ **CR** Costa Rica
- ■ **CU** Cuba
- ■ **CZ** Czech Republic
- ■ **DE** Germany
- ■ **DK** Denmark
- ■ **DM** Dominica
- ■ **DZ** Algeria
- ■ **EC** Ecuador
- ■ **EE** Estonia
- ■ **ES** Spain
- ■ **FI** Finland
- ■ **GB** United Kingdom
- ■ **GD** Grenada
- ■ **GE** Georgia
- ■ **GH** Ghana
- ■ **GM** Gambia
- ■ **HR** Croatia
- ■ **HU** Hungary
- ■ **ID** Indonesia
- ■ **IL** Israel
- ■ **IN** India
- ■ **IS** Iceland
- ■ **JP** Japan
- ■ **KE** Kenya
- ■ **KG** Kyrgyzstan
- ■ **KP** Democratic People's Republic of Korea
- ■ **KR** Republic of Korea
- ■ **KZ** Kazakhstan
- ■ **LC** Saint Lucia
- ■ **LK** Sri Lanka
- ■ **LR** Liberia
- ■ **LS** Lesotho
- ■ **LT** Lithuania
- ■ **LU** Luxembourg
- ■ **LV** Latvia
- ■ **MA** Morocco
- ■ **MD** Republic of Moldova
- ■ **MG** Madagascar
- ■ **MK** The former Yugoslav Republic of Macedonia
- ■ **MN** Mongolia
- ■ **MW** Malawi
- ■ **MX** Mexico
- ■ **MZ** Mozambique
- ■ **NO** Norway
- ■ **NZ** New Zealand
- ■ **PL** Poland
- ■ **PT** Portugal
- ■ **RO** Romania
- ■ **RU** Russian Federation
- ■ **SD** Sudan
- ■ **SE** Sweden
- ■ **SG** Singapore
- ■ **SI** Slovenia
- ■ **SK** Slovakia
- ■ **SL** Sierra Leone
- ■ **TJ** Tajikistan
- ■ **TM** Turkmenistan
- ■ **TR** Turkey
- ■ **TT** Trinidad and Tobago
- ■ **TZ** United Republic of Tanzania
- ■ **UA** Ukraine
- ■ **UG** Uganda
- ■ **US** United States of America
- ■ **UZ** Uzbekistan
- ■ **VN** Viet Nam
- ■ **YU** Yugoslavia
- ■ **ZA** South Africa
- ■ **ZW** Zimbabwe

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

■ Equatorial Guinea GQ ■ OMAN OM ■ TUNISIE TN.
■ Philippines PH. ■ ZAMBIE ZM. □ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 27 December 2000 (27/12/2000)	2,327,527	CA		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* . . . .

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EPO

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of **sheets in paper form:**

request (including declaration sheets)	:	5
description (excluding sequence listing part)	:	49
claims	:	3
abstract	:	1
drawings	:	6
Sub-total number of sheets	:	64
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	64

(b) sequence listing part of description filed in **computer readable form**

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

	Number of items
1. ☒ fee calculation sheet :	1
2. ☐ original separate power of attorney :	
3. ☐ original general power of attorney :	
4. ☐ copy of general power of attorney; reference number, if any: ..... :	
5. ☐ statement explaining lack of signature :	
6. ☐ priority document(s) identified in Box No. VI as item(s): ..... :	
7. ☐ translation of international application into *(language)*: ..... :	
8. ☐ separate indications concerning deposited microorganism or other biological material :	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application) :	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter* :	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column :	
10. ☐ other *(specify)*: ..... :	

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

GOUDREAU GAGE DUBUC

By: Katherine Britt

KATHERINE BRITT

For receiving Office use only

1. Date of actual receipt of the purported international application:

2. Drawings:
☐ received:
☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Ltr
IC | 030846

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
KB/11912.32		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 01/ 01860	21/12/2001	27/12/2000
Applicant		
GENEKA BIOTECHNOLOGY INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCA 01/01860

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates to rRNA-derived cDNA used as an internal standard or control to achieve normalization of hybridization signal detection in microarray biochip technology. Because of its relatively invariant expression across tissues and treatments, 18S and 28S ribosomal RNAs are ideal internal controls for quantitative RNA analysis. A way to circumvent the technical difficulties of using ribosomal RNA as a control, because of its overabundance relative to that of other RNAs, is described and claimed in the present application. Improved methods, arrays and kits comprising arrays and free unlabelled ribosomal probes, are objects of this invention. The unlabelled ribosomal probes are used to compete out the excess of ribosomal nucleics present in a sample wherein all cDNA species of the sample are labelled before being placed in contact with the arrays.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/01860

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHENA M ET AL: "QUANTITATIVE MONITORING OF GENE EXPRESSION PATTERNS WITH A COMPLEMENTARY DNAMICROARRAY" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 270, no. 5235, 20 October 1995 (1995-10-20), pages 467-470, XP000644675 ISSN: 0036-8075 page 467, paragraph 4 -page 469, paragraph 2 --- -/--	1-3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2002	13/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Osborne, H

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 01/01860

C.(Continuation) DOCUMENTS CONSIDERED [redacted] E RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EICKHOFF B ET AL: "NORMALIZATION OF ARRAY HYBRIDIZATION EXPERIMENTS IN DIFFERENTIAL GENE EXPRESSION ANALYSIS" NUCLEIC ACIDS RESEARCH, IRL PRESS LTD., OXFORD, GB, vol. 27, no. 22, 15 November 1999 (1999-11-15), pages E33I-E33III, XP001018017 ISSN: 0305-1048 page E331 ---	1-3
A	WO 00 39339 A (ROSETTA INPHARMATICS INC) 6 July 2000 (2000-07-06) page 11, line 16 -page 14 ---	1-3
A	US 6 057 134 A (GOLDRICK MARIANNA ET AL) 2 May 2000 (2000-05-02) cited in the application -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 01/01860

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0039339 A	06-07-2000	US 6351712 B1	26-02-2002
		AU 2385500 A	31-07-2000
		CN 1335893 T	13-02-2002
		EP 1141411 A1	10-10-2001
		US 2002128781 A1	12-09-2002
		WO 0039339 A1	06-07-2000
US 6057134 A	02-05-2000	NONE	